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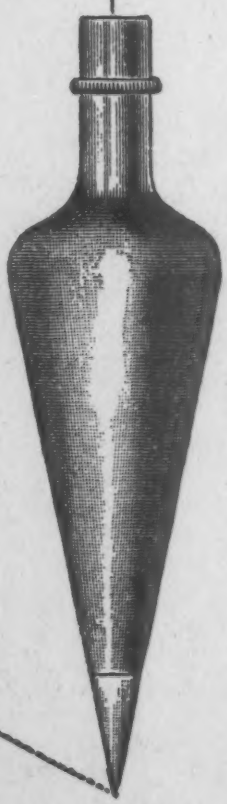

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CARCINOMA OF THE BREAST*

A STUDY OF 298 CONSECUTIVE CASES

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THE TREATMENT OF CANCER of the breast has been the subject of careful study for the past 50 years, since Halsted first described his radical operation. Nevertheless, there is still considerable confusion as to whether surgery alone, or a combination of surgery and roentgen therapy will prove more beneficial. Also, the place of androgenic hormones in the treatment of both the primary lesion and metastases is still in the experimental stage. The fact that there is no unanimity of opinion on the proper steps to be taken when a case of cancer of the breast presents itself to the surgeon is well-known. This condition was emphasized by Trimble in his paper published in 1940. He quotes from personal communications from the heads of nine of the important clinics in this country. These replies not only show that there is no one pattern which is universally accepted as the most effective therapy, but also indicates that there is a wide variation in the relative importance attached to radical amputation, the use of pre- and postoperative radiation, and castration, whether accomplished surgically, by roentgen ray, or through the use of hormones.

It should also be added that the operation for the radical removal of the breast for cancer varies a great deal with different surgeons. Some operators will be content with the removal of the breast, together with the pectoral muscles and most of the axillary contents. Many times the dissection of the axillary contents is not carried out with meticulous care, so that every possible shred of tissue that may harbor malignant cells is removed.

Because of the rather confused state of handling cancer of the breast, and the belief that the only way to obtain some firm basis for therapy is by accurate and critical analysis of the results of any particular method of treatment, a study of a consecutive series of cases was undertaken. The series

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contains all the cases operated upon at the Union Memorial Hospital, in Baltimore, through the 15-year period 1930–1945, by four surgeons; namely, J. M. T. Finney, Sr., William A. Fisher, John M. T. Finney, Jr., and one of the authors (G. G. F.). The first and last named of these surgeons participated for nine and eleven years, respectively, while the other two participated for the full fifteen.

The cases are all private female patients who were referred by their own physicians, or who presented themselves directly to the surgeon. There are no clinic cases in this series. Each case has been proved to have a definite cancer of the breast by pathologic examination, both gross and microscopic, by one of the authors (W. C. M.), who is the Pathologist at the Union Memorial Hospital. No case has been included which comes in a precancerous or equivocal category. Likewise, no case has been omitted because none has been refused the benefit of treatment and so left out of the series. Because of the fact that this study was not undertaken to prove any particular point, but simply to evaluate the results as they were found, the consecutive cases of these four surgeons were studied because it was felt that this group would represent the same general concept in the treatment of cancer of the breast. This concept is founded on the belief that with our present state of knowledge, it is paramount that the radical removal of the breast be carried out with the strictest attention to detail in every step of the operation, at the earliest possible moment after a definite diagnosis of cancer has been made. The type of operation that has been done in the vast majority of these cases is a modification of the original Halsted operation, and often referred to as the closed plastic operation. An excellent description of this operation was included by Trimble in his paper referred to above, so the details will not be given here. However, it does seem important to point out certain essential steps that should be reëmphasized:

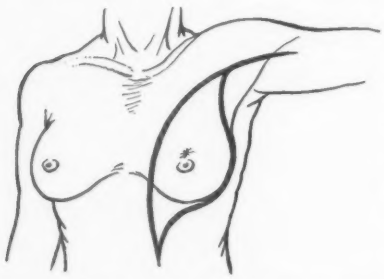

FIG. 1.—Type of incision used in all cases of radical amputation.

1. The cardinal principles of good surgery, namely: the gentle handling of tissue, complete hemostasis, and absolute asepsis, are essential.

2. In making the initial incision, the operator is guided in the amount of skin that is taken solely by the size and location of the tumor, and not with any thought to closure of the wound. The incision is illustrated in Figure 1.

3. Great care is taken to cut the skin flaps thin and evenly, so that there will be a minimum amount of subcutaneous tissue left.

4. After division of the insertion of the pectoralis major and minor muscles, the axillary contents are completely removed by sharp dissection, leaving the axillary vessels absolutely clean, as shown in Figure 2.

5. The complete removal of the entire breast, together with the pectoral

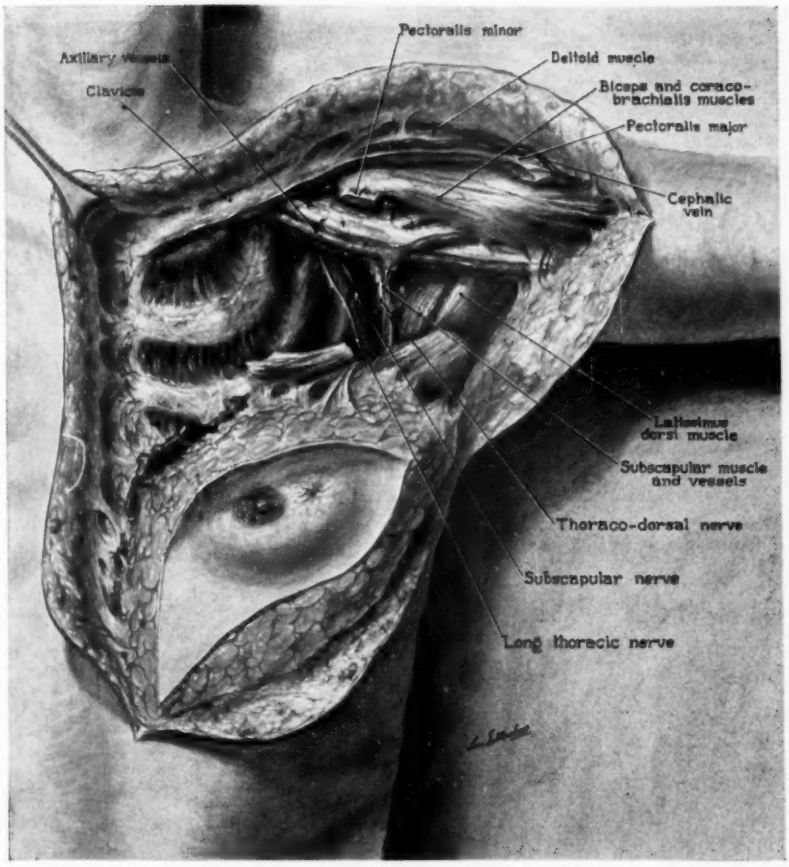

FIG. 2.—Artist's composite drawing of radical amputation showing extent of dissection.

muscles and the upper border of the sheath of the rectus muscle in one mass, leaving the chest wall clean.

6. The thorough washing out of the wound with warm normal salt solution before closure, and a thorough check to assure the removal of any extraneous tissue that may have been left and complete hemostasis.

7. In the vast majority of cases, the wound can be closed without undue tension, and grafting is unnecessary. When a graft is necessary, the Ollier-Thiersch type is used and immediately applied.

TABLE I

TOTAL AMOUNT OF ROENTGEN RAY THERAPY

Preoperative treatment	7
Postoperative treatment	14
Sterilization	6
Treatment of late metastases	36
Total number of cases treated	63

Two of the patients who had preoperative irradiation received a course postoperatively as well. Also two patients who were sterilized by roentgen ray had a postoperative course of treatment to the operative site. There was one patient who was sterilized surgically beside the six shown above.

TABLE II

PATHOLOGIC CLASSIFICATION OF CASES

Group I	Duct cell—with and without chronic cystic mastitis	171
Group II	Duct cell—comedo in productive mastitis	32
Group III	Duct cell—Paget's disease	6
Group IV	Cystadenocarcinoma	33
Group V	Adenocarcinoma	41
Group VI	Mucoid or colloid carcinomas	4
Group VII	Acute carcinosis	3
Group VIII	Miscellaneous group	8
Total cases		298

8. All wounds are drained through a stab-wound laterally, about the level of the midportion of the incision.

As stated above, radical surgery has been the essential form of treatment in this group of cases, although both preoperative and postoperative irradiation has been used in a few of the cases as shown in Table I. Four of the patients who received preoperative irradiation had received this therapy before being referred to the surgeon. The other three were cases who had far advanced lesions and in one of these ulceration of the skin had already taken place by the time the patient sought surgical advice, so a course of irradiation was given before these patients were submitted to surgery. Sterilization as a therapeutic measure has been used in seven patients and it has been recommended

in a number of other instances where the patient declined to submit to it. It is interesting to note that in this series of 298 cases, some 222, or 74 per cent, had already passed the menopause. The use of androgenic hormones in this series has been limited to three cases that had already developed metastases, and they are under treatment at the present time.

In analyzing any series of data from a group of cases, it is readily seen that it can be broken down in many different ways. In this report an attempt

TABLE III

AGE DISTRIBUTION

	30–40	40–50	50–60	60–70	70–80	80–90
Group I	11	43	45	48	18	4
Group II	7	7	7	8	3	0
Group III	0	1	2	3	0	0
Group IV	2	5	10	8	7	1
Group V	4	10	10	14	3	0
Group VI	1	0	1	2	0	0
Group VII	0	0	0	2	1	0
Group VIII	1	2	8	2	1	0
Total	26	68	77	87	33	5

Unknown—2

TABLE IV

MARITAL STATUS

	Married	Single
Group I	128	43
Group II	24	8
Group III	4	2
Group IV	29	4
Group V	35	6
Group VI	1	3
Group VII	2	1
Group VIII	6	2
Total	229	69

TABLE V

TIME-LAPSE FROM DISCOVERY TO TREATMENT

2 weeks 69	1 year 31	5 years 4	15 years 2
1 month 44	2 years 24	6 years 3	16 years 1
3 months 55	3 years 9	8 years 1	17 years 1
6 months 43	4 years 2	10 years 2	20 years 1

Unknown—6

will be made to submit tables that will show as clearly and accurately as possible the most important features. Of these 298 cases, it has been possible to get accurate follow-up data on 280, or 94 per cent. There were three patients who died following operation before they left the hospital, and are, therefore, considered operative deaths. This gives an operative mortality of approximately 1 per cent.

It was felt that a careful classification from the pathologic standpoint would be very interesting and important, particularly if any correlation

between the different groups and ultimate results developed. Table II gives the pathologic classification of all the cases studied. Group I, of course, contains the largest number, and it was interesting to note that at least 73 cases of the total showed definite chronic cystic mastitis. In Group IV there were included all those cases where the tumor developed from intraductal papillomas, from the epithelial lining of cysts, and also from sweat glands. In Group V, there were those tumors that developed from fibroadenomas, as well as the acinar type. In Group VIII were gathered all those tumors that

TABLE VI

BREAST INVOLVED

	Left	Right
Group I	95	82
Group II	21	11
Group III	4	2
Group IV	21	12
Group V	24	17
Group VI	2	2
Group VII	1	2
Group VIII	7	1
Total	175	129

Bilateral—6

TABLE VII

LOCATION OF TUMOR

	Upper Outer Quadrant	Upper Inner Quadrant	Lower Outer Quadrant	Lower Inner Quadrant	Upper Half	Lower Half	Outer Half	Central	Whole Breast
Group I	87	15	19	11	14	6	4	16	2
Group II	17	1	3	3	3	0	2	2	1
Group III	1	0	0	0	0	0	0	4	0
Group IV	17	4	2	1	3	1	3	1	0
Group V	18	8	3	1	3	1	4	1	0
Group VI	2	0	1	0	0	0	0	0	1
Group VII	1	2	0	0	0	0	0	0	0
Group VIII	1	2	3	0	0	0	0	0	1
Total	144	32	31	16	23	8	13	24	5

Unknown—8

did not definitely fit in one of the other seven groups. Simply for the purpose of illustrating each group as we have arranged them, we have included as examples the photomicrographs shown here.

Table III shows the age distribution of the cases, and this follows quite closely the pattern shown in many other important series, except for the fact that the peak is reached in the age-group of 60–70 years, rather than the decade of 50–60. In this series there was no patient in the second decade of life, while there were two patients 31 years of age, the youngest recorded. It is interesting to note that 14 of the 30–40 age-group had evidence of microscopic metastases in the axillary nodes at the time of operation, and only

two of these are still alive, one ten years since operation, and the other two. In this age-group, of the 12 who did not show microscopic metastases in the axillary nodes at the time of operation, five have died with metastases, while the remaining seven have been alive and well for an average of seven years, with the longest 14, and the shortest, two years' duration.

Table IV gives the marital status of the patients, and shows that the ratio is about the same as that which has been found in other reported series.

Table V is not only a very interesting one, but it is also quite shocking, when it is realized that 50 patients had known that they had a lump in the breast for at least two years, or more, and an additional 31 had known of the

TABLE VIII

RELATION OF LOCAL RECURRENCE TO GRAFTING AT OPERATION

Number of Thiersch grafts		28
Number of local recurrences		18
(a) In grafted cases	3	
(b) In cases not grafted	15	
(c) In cases with microscopic metastases at time of operation	10	
(d) In cases with no microscopic metastases at time of operation	8	

presence of a lump for at least a year. There were many different explanations by the patients as to why they had delayed so long before seeking surgical attention, but there were two main reasons that stood out. The first was the fear that the lump in the breast might prove to be serious, and, therefore, the patient confided her trouble to no one. The second was the fact that the patient had consulted her local medical doctor soon after discovery of the tumor, but after being examined, she had been assured that there was no cause to fear any trouble. Consequently, most of these patients had done nothing until the tumor had obviously increased in size, or until the advent of pain, usually of a sharp sticking quality, had caused them to seek relief. There

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FIG. 3.—Duct cell carcinoma showing a marked fibrous reaction representative of Group I.

FIG. 4.—Carcinoma of the ducts, comedo type. Note the marked proliferation of epithelium and distention of ducts.

FIG. 5.—Paget's Disease of the nipple with carcinoma, showing the transition from the non-ulcerated epidermis into the eroded part of the growth. The vacuolated Paget's cells can be seen by low magnification.

FIG. 6.—Papillary carcinoma. The wall of the cyst can be seen at the margin of the photograph. This patient had metastasis to the axillary glands.

FIG. 3

FIG. 4

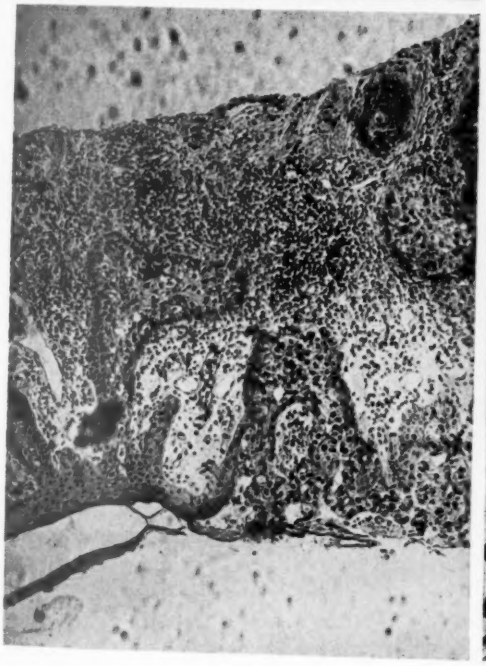

FIG. 5

FIG. 6

were also many women who were lulled into false security, even though they knew they had a lump in the breast, by the fact that for some time they had had no pain or discomfort, and, therefore, felt there was no cause for alarm.

Table VI gives the relative frequency of involvement of each breast, and it also shows that in this series of cases there were six patients who had bilateral cancers. In these patients the time-interval between involvement of

TABLE IX

CONSOLIDATED VITAL STATISTICS OF ALL PATIENTS

No. of Years	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Total
Alive and Well:	0	23	21	11	12	16	7	11	7	7	8	6	5	6	10	150
No. with microscopic metastases at time of operation	0	9	4	4	4	4	2	3	3	3	4	0	2	1	2	45
No. without microscopic metastases at time of operation	0	14	17	7	8	12	5	8	4	4	4	6	3	5	8	105
Died with Metastases:	15	25	24	18	10	5	4	3	3	5	0	2	0	1	1	116
No. with microscopic metastases at time of operation	12	18	15	12	5	2	2	0	0	2	0	1	0	1	1	71
No. without microscopic metastases at time of operation	3	7	9	6	5	3	2	3	3	3	0	1	0	0	0	45
Alive with Metastases:	0	2	1	3	1	1	0	1	1			1				11
No. with microscopic metastases at time of operation	0	2	1	0	0	1	0	1	1			1				7
No. without microscopic metastases at time of operation	0	0	0	3	1	0	0	0	0			0				4
Total number of cases																277

TABLE X

CONSOLIDATED VITAL STATISTICS OF GROUP I

No. of Years	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Total
Alive and Well:	0	15	12	6	5	10	1	2	6	5	4	3	0	3	9	81
No. with microscopic metastases at time of operation	0	6	4	3	3	3	0	1	3	2	2	0	0	1	2	30
No. without microscopic metastases at time of operation	0	9	8	3	2	7	1	1	3	3	2	3	0	2	7	51
Died with Metastases:	8	13	18	10	6	3	2	3	1	4	0	1	0	1	1	71
No. with microscopic metastases at time of operation	6	11	12	8	5	2	2	0	0	2	0	1	0	1	1	51
No. without microscopic metastases at time of operation	2	2	6	2	1	1	0	3	1	2	0	0	0	0	0	20
Alive with Metastases:	0	2	1	2	0	1	0	1								7
No. with microscopic metastases at time of operation	0	2	1	0	0	1	0	1								5
No. without microscopic metastases at time of operation	0	0	0	2	0	0	0	0								2
Unknown	10															
Operative mortality	2															

the first breast and the second one was eight months, one year, two years, three years, ten years, and 16 years, respectively.

The pattern of the location of the tumor in the breast is shown in Table VII. In this group of cases, as in many other reported series, the predilection of the upper outer quadrant of the breast as the site of involvement is most striking. In fact, this area contained nearly half of the tumors in the entire series.

Let us now turn to the results that we have found in studying this consecutive series of cases. As has been stated above, we have been able to obtain accurate follow-up data on 280 of the original group of 298. The majority of the 18 that could not be traced had come for operation from other cities and contact with them has been lost. It does not seem fair to presume that all of this group have died. It is more likely that they would fit

TABLE XI

CONSOLIDATED VITAL STATISTICS OF GROUP II

No. of Years	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Total
Alive and Well:	0	2	2	0	1	3	2	2	0	1	0	1	0	1	0	15
No. with microscopic metastases at time of operation	0	0	0	0	0	1	2	0	0	1	0	0	0	0	0	4
No. without microscopic metastases at time of operation	0	2	2	0	1	2	0	2	0	0	0	1	0	1	0	11
Died with Metastases:	3	4	2	1	0	2	0	0	1	0	0	0	0	0	0	13
No. with microscopic metastases at time of operation	3	3	1	1		0			0							8
No. without microscopic metastases at time of operation	0	1	1	0		2			1							5
Alive with Metastases:									1			1				2
No. with microscopic metastases at time of operation									1			1				2
No. without microscopic metastases at time of operation									0			0				0
Unknown	2															
Operative mortality	0															

TABLE XII

CONSOLIDATED VITAL STATISTICS OF GROUP IV

No. of Years	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Total
Alive and Well:	0	2	3	4	0	2	2	2	0	1	1	1	2	0	0	20
No. with microscopic metastases at time of operation	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	2
No. without microscopic metastases at time of operation	0	2	3	4	0	2	2	1	0	1	0	1	2	0	0	18
Died with Metastases:	0	4	1	3	1	0	0	0	1	1	0	0	0	0	0	11
No. with microscopic metastases tases at time of operation	0	3	0	1	0				0	0						4
No. without microscopic metastases at time of operation	0	1	1	2	1				1	1						7
Unknown	2															
Operative mortality	0															

into the same general pattern shown by the series as a whole. However this may be, the results of the 277 followed are shown in the following Tables. It has been thought by some surgeons that the incidence of local recurrence following radical mastectomy is usually higher when skin grafting is not made a routine part of the operative procedure. In Table VIII it will be seen that in this series of cases Thiersch grafts were found necessary in 28 cases. In the 280 cases that have been followed there were 18 local recurrences, which is an incidence of approximately 6 per cent. There were three local recurrences in the grafted cases, or an incidence of a little more than 10 per cent,

while there were 15 recurrences in the cases that were closed, or a little less than 6 per cent. It seems that the most important step in preventing local recurrence is the removal of an adequate amount of skin. This, however, does not imply that the application of a graft will be necessary for proper closure.

Table IX is perhaps the most interesting and instructive one of this series. Here the results have been broken down into the three main categories of *Alive and Well, Died with Metastases,* and *Alive with Metastases,* for each

TABLE XIII

CONSOLIDATED STATISTICS OF GROUP V

No. of Years	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Total
Alive and Well:	0	3	4	1	5	1	2	2	1	0	2	1	1	1	1	25
No. with microscopic metastases at time of operation	0	2	0	1	2	0	0	0	0	0	1	0	1	0	0	7
No. without microscopic metastases at time of operation	0	1	4	0	3	1	2	2	1	0	1	1	0	1	1	18
Died with Metastases:	2	3	2	2	2	0	0	0	0	0	0	0	0	0	0	11
No. with microscopic metastases at time of operation	1	1	1	1	0											4
No. without microscopic metastases at time of operation	1	2	1	1	2											7
Alive with Metastases:				1	1											2
No. with microscopic metastases at time of operation				0	0											0
No. without microscopic metastases at time of operation				1	1											2
Unknown	3															
Operative mortality	0															

of the 15 years of the study. At the same time there is shown the number of patients in each of these three categories who either showed the presence of microscopic metastases at the time of operation, or whose nodes were as yet free from metastasis. It can be readily seen that of the 150 patients who have been alive and well for the varying number of years shown, there were 105 who did not have microscopic metastases in the axillary nodes at the time of operation, as compared with only 45 who did. Of the 116 who have already

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FIG. 7.—Acinar cell carcinoma. The cells have a tendency to pool, forming pseudo-acinar patterns.

FIG. 8.—Carcinoma arising in a fibroadenoma. The encapsulation of the growth is seen in the corner of the photograph. This patient also had metastasis and most of the growth was well encapsulated.

FIG. 9.—Mucoid carcinoma. Clumps of epithelian cells are suspended in pools of a gelatinous substance.

FIG. 10.—Acute carcinosis. The entire breast is involved, accompanied by a marked lymphocytic reaction. History of rapid enlargement of the breast over a period of six weeks.

FIG. 7

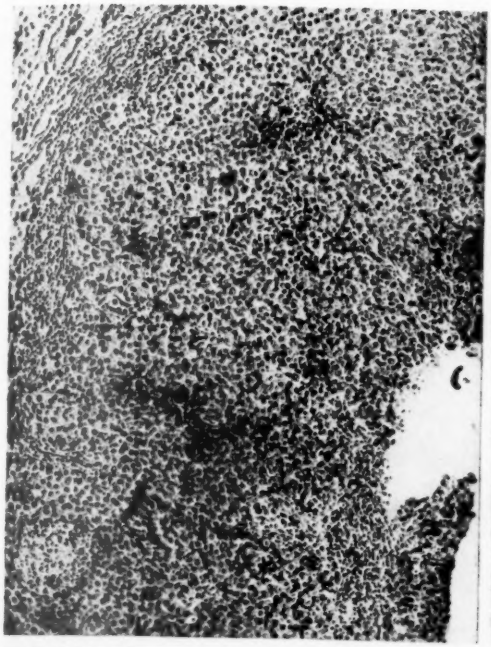

FIG. 8

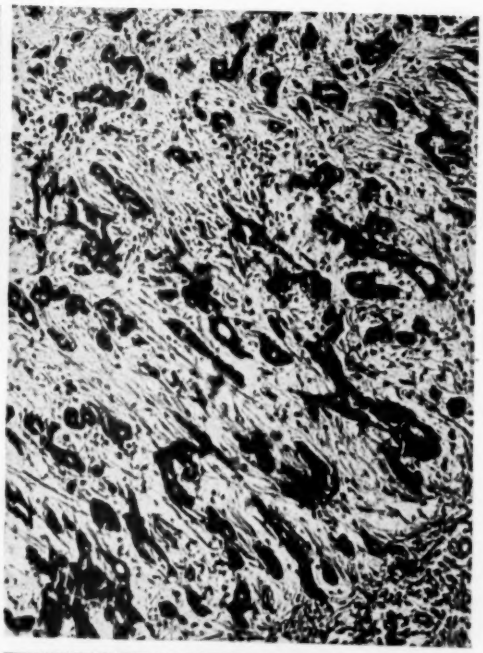

FIG. 9

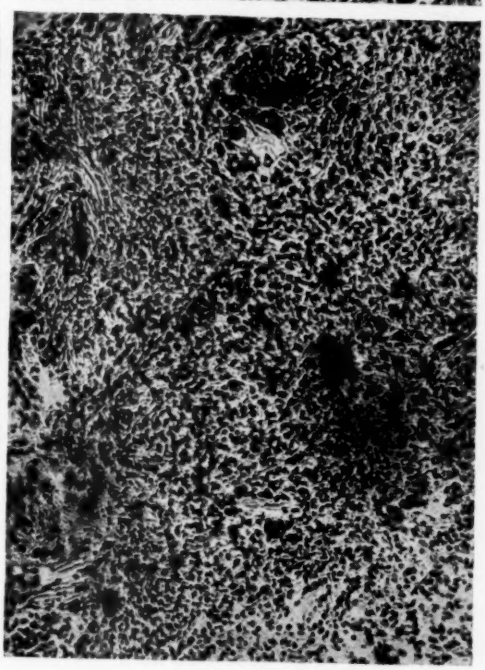

FIG. 10

died with metastases at the end of the varying number of years, as shown in Table IX, 71 had microscopic metastases when radical amputation was done, and 45 did not have any evidence of microscopic metastases at operation but, nevertheless, developed metastases later and died. It should be noted that two patients who had microscopic metastases in their nodes at the time of oper-

TABLE XIV

RESULTS IN ALL CASES

Years after Operation	Number under Observation on this Anniversary	Percentage of Total	Number not followed beyond this Year	Died within this Anniversary Year
1	277	100	0	15
2	262		24	25
3	213	77	22	24
4	167		15	17
5	135	49	14	10
6	111		17	5
7	89		7	4
8	78		12	3
9	63		8	3
10	52	19	8	5
11	39		7	0
12	32		7	2
13	23		5	0
14	18		6	1
15	11	4	10	1

TABLE XV

RESULTS IN GROUP I

Years after Operation	Number under Observation on this Anniversary	Percentage of Total	Number not followed beyond this Year	Died within this Anniversary Year
1	259	100	0	8
2	151		17	13
3	121	77	13	18
4	90		8	10
5	72	45	5	6
6	61		11	3
7	47		1	2
8	44		3	3
9	38		6	1
10	31	19	5	4
11	22		4	0
12	18		3	1
13	14		0	0
14	14		5	1
15	10	6	9	1

ation are still alive and well after 15 years, while two other such patients had lived for 13 and 14 years, respectively, before dying of metastases. All four of these patients showed tumors of duct cell origin.

Tables X, XI, XII and XIII show results in Groups I, II, IV and V. Because of the small number of cases in the other four groups, these are not included.

Table XIV shows quite graphically what has happened to the 277 patients who have been adequately followed. Column 4 entitled "Number not followed beyond this Year," contains all cases who died of some cause other than cancer, of which there was a total of 23. Of these 23 patients, 15 lived one to five years, four lived six to ten years, and the remaining four

TABLE XVI

RESULTS IN GROUP II

Years after Operation	Number under Observation on this Anniversary	Percentage of Total	Number not followed beyond this Year	Died within this Anniversary Year
1	30	100	0	4
2	27		2	2
3	21	70	2	1
4	17		0	0
5	16	52	1	2
6	15		3	0
7	10		2	0
8	8		2	1
9	6		1	0
10	4	13	1	0
11	3		0	0
12	3		2	0
13	1		0	0
14	1		1	0
15	0	0	0	0

TABLE XVII

RESULTS IN GROUP IV

Years after Operation	Number under Observation on this Anniversary	Percentage of Total	Number not followed beyond this Year	Died within this Anniversary Year
1	31	100	0	0
2	31		2	4
3	25	81	3	1
4	21		4	3
5	14	45	0	1
6	13		2	0
7	11		2	0
8	9		2	0
9	7		0	1
10	6	19	1	1
11	4		1	0
12	3		1	0
13	2		2	0
14	0		0	0
15	0	0	0	0

lived between 11 and 15 years. This column also contains in each year the corresponding number of cases still living who have not been operated upon for a longer period. The column entitled "Died within this Anniversary Year" contains all those cases, but only those cases who died of metastases within each year. It can be seen, therefore, that in order to determine the total

number of patients who have survived at the end of each year, the sum of the "Number not followed beyond this Year" and the number who "Died within this Anniversary Year" is subtracted from the "Number under Observation on this Anniversary." When we have in this way obtained the number of patients who are under observation at the end of each of the 15 years, we can readily determine the per cent who have survived death either from metastases, or any other cause. In Tables XV, XVI, XVII and XVIII it is interesting to see how closely the survival rates parallel each other in spite of the difference in the tumors from the pathologic standpoint.

SUMMARY

1. A consecutive series of 298 cases of cancer of the breast operated upon during the 15-year period 1930–1945 has been studied.

TABLE XVIII

RESULTS IN GROUP V

Years after Operation	Number under Observation on this Anniversary	Percentage of Total	Number not followed beyond this Year	Died within this Anniversary Year
1	39	100	0	3
2	36		3	3
3	30	77	4	2
4	24		2	2
5	20	51	6	2
6	12		1	0
7	11		2	0
8	9		2	0
9	7		1	0
10	6	15	0	0
11	6		2	0
12	4		1	0
13	3		1	0
14	2		1	0
15	1	3	1	0

2. A complete follow-up has been obtained in 280 cases.

3. All cases were treated surgically with 281 radical mastectomies and 17 simple mastectomies by four surgeons with an operative mortality of 1 per cent.

4. Only 19 patients received either pre- or postoperative radiation to the tumor site, while seven patients of the premenopausal group were sterilized following radical mastectomy.

5. Hormonal therapy has been used in only three cases, all of whom have metastatic lesions.

6. Of the 150 patients who did not die of cancer metastases, 70 per cent showed no metastatic lesions in their axillary nodes at the time of operation, while 30 per cent showed metastases.

7. In this series the survival rates were 77 per cent after three years, 49 per cent after five years, 19 per cent after ten years, and 4 per cent after 15 years.

8. Radical operation before metastasis has occurred in the axillary nodes gives the best prognosis.

9. A plea is made for the reporting of complete and accurate results of treatment of cancer of the breast so that proper evaluation can lead to better results.

10. Further education is necessary to insure better results in the future.

REFERENCE

1 Trimble, I. R.: Surgery, Gynecology and Obstetrics, 70, 82–92, January, 1940.

CARCINOMA OF THE BREAST: RESULTS OF COMBINED TREATMENT WITH SURGERY AND ROENTGEN RAYS*

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SINCE THE INTRODUCTION of radical surgical treatment for cancer of the mammary gland by Halsted and Willy Meyer, radical mastectomy has been the method most commonly employed by the medical profession to treat patients with this type of malignancy. In spite of the fact that radical dissection has approached the acme in the thoroughness of removal of the mammary gland, with its tumor and the surrounding structures of the chest wall and axilla, yet the five-year clinical survival rate has remained relatively stationary and the reported results of treatment of breast carcinoma in the literature has shown a discouraging lack of improvement in the number of patients surviving five years after radical operation.

Carcinoma of the breast in the female, like carcinoma of the female pelvic organs, is one of the most frequent causes of death resulting from malignancy. The United States Bureau of Vital Statistics gives a death rate of 12 per 100,000, and the yearly death rate from this type of malignant disease is approximately 16,000 (Table I).

This high death rate from cancer of the breast each year is a direct challenge to the medical profession and the divergent opinions as to the best method of treating an operable cancer of the breast are evidence of the dissatisfaction with the low survival rate after various methods of treatment. Every effort to increase the salvage of these patients, whether by operation or irradiation, is worth the greatest consideration.

That our experience with postoperative results at the Lahey Clinic has been quite similar to other published results is illustrated by a review of a series of patients operated upon prior to 1936 in this Clinic. Only 38.6 per cent of all patients having radical mastectomy (the majority of this group had no irradiation treatment) survived operation five years or more. These results very closely parallel the figures on results given by Haagensen and Stout[6] in the treatment of patients with carcinoma of the breast at the Presbyterian Hospital, in New York, over a period of 20 years; they reported a five-year clinical cure of 36.1 per cent after radical mastectomy.

With these facts in mind and since we could apparently not hope, at least in our hands, to improve the survival rate of patients with surgical removal

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alone, no matter how radically or how skillfully the operation could be done we added to the already radical amputation of the breast, a course of intensive and thorough roentgen therapy applied after operation. Accordingly, beginning in 1935, a uniform method of treatment was outlined and employed whenever possible for all patients with breast carcinoma coming to the Lahey Clinic. This method has been used routinely by us since 1935. It is our purpose in this paper to report the results obtained in this group of patients who have thus been treated, dating from 1935 to 1941, and who have survived a minimum of five years, or longer, without recurrence of tumor. From these results we hoped to draw some conclusions relating to the value or disadvantage of this type of combined treatment. In brief, the treatment has consisted of a Halsted-type of radical amputation of the breast followed by intensive roentgen therapy given in divided doses.

During this period (1935–1941) 283 patients with carcinoma of the breast have received some type of treatment, either radical or simple mastectomy, with irradiation, or some other form of palliative treatment, and of this group, 238 patients have had the complete treatment, that is, radical operation followed by intensive irradiation. Twenty-eight patients have had simple mastectomy, many of whom also had roentgen therapy after operation. It is that group of patients (238) who received the combined method of treatment of radical surgery and irradiation, however, with which we are most concerned in this review.

Although this series of patients is relatively small (238) compared to reports of some larger series of patients, we believe this study to be of value, since these patients have all received the same type of treatment and have been carefully followed and thoroughly studied; and from these data we believe we are justified in attempting to draw some conclusions regarding the efficacy of this combined treatment.

Since 1942 a much larger group of patients has been similarly treated but these patients have been treated too recently to report five-year survival.

In this series we have not attempted to confine our treatment to a selective group of cases that would present a more favorable prognosis but have employed radical operation in all cases in which the cancer was still confined to the breast and to the corresponding axilla. In fact, subsequent pathologic examination of axillary nodes was positive for axillary extension in 62 per cent of the cases. The only contradindication to radical surgery was evidence of distant metastatic spread, involvement of the pleura, of the lungs, bones, or extension to the supraclavicular region.

In general, the radical operative procedure employed has been the method advocated by Halsted, with minor modifications. It has consisted of removal in one block of the breast with its overlying skin, together with excision of the pectoralis major and minor muscles and thorough dissection of axillary contents and fatty and fibrous tissue of the chest wall, including a considerable portion of fascia covering the rectus muscle.

Many types of incisions have been employed by various surgeons; all have

proved useful and each is probably advantageous in the hands of the particular surgeon who is accustomed to his own type of radical mastectomy. The type of incision employed depends to a large measure upon the location of the tumor in the breast. We have used the incision that Halsted later adopted instead of the incision extending out upon the arm which he first described in his earliest report on radical removal of the breast.

FIG. 1.—Operative wound ten days after radical mastectomy. Incision consists of encircling incision, with incision extended vertically above and below the breast. Note extent of range of motion and primary wound healing ten days after operation. Deep radiation therapy can be started immediately at this stage.

This incision consists of a circular incision about the breast with a vertical incision extending above and below the breast, which, in the majority of cases, permits complete access to the contents of the axilla and chest wall.

The extension of the incision on the arm is unnecessary for exposure of the axillary contents and is likely to result in a contracted scar in the axilla, which may greatly limit return of arm motion. Stewart's simple transverse incision is often useful, and permits sufficient exposure of axillary contents and

allows an easy plastic closure of the wound. It is particularly valuable for tumors located in the extreme lateral border of the breast. Greenough's arrowhead incision permits an excellent approach to the axilla in those tumors which arise high in an axillary extension of the breast, where it may be used most advantageously. We have intentionally limited the extent of the skin excised, removing the skin over the breast and placing the line of skin incision about 5 to 6 cm. from the border of the tumor. This has been done in an effort to obtain a primary plastic closure of skin over the chest wall in order to obtain early healing so that irradiation treatment could be started immediately after radical operation (Fig. 1). Roentgen therapy is started as early as possible, in most cases within eight or ten days after operation. We have thought that wide excision of skin would involve closure of the defect with immediate Thiersch graft, which would greatly prolong healing and seriously delay the institution of radiation therapy.

There are few cases, indeed, in which radical mastectomy cannot be done with a great margin of safety. In this group there was only one postoperative death, which resulted from a coronary occlusion. Following radical mastectomy, these patients are allowed up in a chair on the second or third day. They are encouraged to exercise the arm early and before radiation treatment is started almost all have complete range of motion.

Simple mastectomy has been employed in 28 patients, and only in those patients whose constitutional condition would not permit a radical surgical procedure; in some it was used to remove a large ulcerating lesion or as a palliative procedure in advanced malignancy. Of this group of 28 patients only three have survived five years, and this is to be expected since this operation, in main, was employed palliatively in advanced cancer. In view of the fact that a fairly large group of patients (37 per cent in this report) with axillary involvement can be salvaged by radical mastectomy, there is no logical reason to employ simple mastectomy as a method of routine treatment, as is advocated by many surgeons, and such a method of treatment is to be heartily condemned. Particularly is this true with early carcinoma of the breast, as it is at this time that carcinoma should be treated most vigorously and radical operation has the greatest opportunity to accomplish a cure.

It is unnecessary to state that employment of postoperative roentgen therapy does not represent a new method of treatment as the literature[12, 13] contains many reports of groups of patients treated with roentgen rays postoperatively, but with few exceptions the roentgen dosage has been small, or has been unrecorded, and seldom has there been reported a series of cases in which a uniform method of such combined treatment has been employed.

IRRADIATION TREATMENT

In 1935, when high voltage shock-proof roentgen-ray equipment became available, it was our opinion that the value of postoperative radiation for carcinoma of the breast was a debatable question. The seriousness of the disease in question, the need of more vigorous treatment and the frequency

of recurrence of the disease made it seem feasible to outline a course of treatment to be given as soon after operation as was possible and to run a series of cases in which operation and radiation would be on a routine basis. The surgical plan which was carried out on this series has been given. Radiation treatment was started within ten days to two weeks following the operation, when we deemed the healing of the wound was satisfactory. Treatment was delivered to the scar, axillary and supraclavicular regions. In all cases a uniform plan of treatment was carried out, using the following factors: 200 k.v.p., 1 mm. copper filtration, distance 50 cm., portal size 15 cm. round cone, daily dose 300 r. As the initial dose 300 r was given to each port treating one portal daily for three days. Following this, each portal was treated daily with 100 r, until 2,400 r had been delivered to each of three portals for an over-all dose of 7,200 r, all measurements taken in air. By giving this postoperative radiation in this manner, there was no material interference with wound healing. There was only a moderate skin reaction to the roentgen-rays, and there were no resulting pulmonary changes, such as radiation pneumonitis. The erythema and desquamation which do occur following this form of treatment are limited to the axilla and scar regions, reach a peak between 15 and 21 days, and the erythema gradually fades off until the skin is normal except for pigmentation at the end of eight weeks. No local treatment other than vaseline or boric acid ointment is necessary to control the effects of radiation dermatitis. The patient's course should be followed in three weeks after treatment to determine the degree of erythema and any complications which may have arisen from the radiation treatment, and, again, at the eight-week period for a review of the entire problem, at which time fluoroscopy of the chest should be done to rule out radiation pneumonitis.

It is apparent from a study of our results that the combined treatment was not successful in controlling recurrence of the disease in 25 per cent of the cases, even when the disease was clinically limited to the breast region. It was unsuccessful in controlling the disease in 62 per cent of those cases in which the disease had already spread to the axilla before operation. A glance at the location of the metastatic disease, however, indicates that there was very little local recurrence or persistence of the disease unless it had spread to regional lymph nodes prior to treatment.

COMPLICATIONS OF RADIATION TREATMENT

The most frequent complication of radiation treatment is nausea, and often this is associated with vomiting. This complication may usually be avoided by giving a high caloric diet, by delaying treatment for a day or two or by decreasing the daily dose. It was not necessary to decrease the daily dose except in a very few cases.

In all cases there was a moderate skin reaction consisting of erythema and in most cases desquamation of the skin beneath the axilla where the skin from the arm rubs against the skin of the chest wall. In no case was this a serious complication; however, it should always be explained to the patient that this

is going to occur and that proper healing will take place in eight weeks' time. One severe complication which follows radiation treatment over the chest wall is radiation pneumonitis, which has been entirely avoided in this series by treating with small daily doses; with realization that this may occur, it should be pointed out that the differential diagnosis is between true pneumonia, radiation pneumonitis, and secondary malignancy. It is further necessary to emphasize that these changes in the lung should never be treated by further radiation even though it should prove later on to be a recurrence of the disease, especially if the pulmonary changes come within 120 days following treatment.

In radiation pneumonitis, coughing is likely to be severe and may be difficult to control even with large doses of codeine, and in some instances heroin has been used to control the cough. In the cases in which we have seen radiation pneumonitis the effects of the disease gradually disappeared in about 90 days, or less, leaving a residual fibrosis and atelectasis of the lung involved. with disappearance of cough.

PALLIATIVE RADIATION TREATMENT

The radiation treatment for carcinoma of the breast other than for postoperative localized treatment is delivered as a palliative measure for recurrence in the skin, nodes, bone or abdomen. Lesions in the lungs are usually refractory to treatment and lesions involving the cranial vault, unless small and localized, are probably best not treated unless the patient understands that the hair is to be removed as a result of treatment.

The quantity of roentgen-rays necessary to bring about relief of pain from bone lesions is relatively small and should not be given in large enough dosage to produce roentgen sickness or complications of treatment. We use a maximum of 1800 r to each area and never treat a portal larger than a 15 cm. round cone in order to avoid radiation sickness and skin damage. It is generally recognized that if the lesion is hematogenous in type and involving bone, a cure is almost impossible, although there have been several reported cases of patients living for five years, or more.

When the spread of disease is lymphatic and localized to skin a single large dose of roentgen-rays may be used if the lesion is not larger than 2 cm. It must be recognized that spread has likely taken place through other lymphatic channels before treatment is given, and many times it has spread some distance from the first-noted lesion, but it is always advisable to include at least 1 cm. of skin in the field to be irradiated in order to block-off lymphatics, and, thereby, stop further lymphatic spread. It is our custom to shield the remaining skin with 0.5 mm. of lead and treat with a small cone. We use superficial radiation treatment, 90 k.v.p., 20 cm. distance, and give 2,400 r measured in air at one sitting. If the lesion is larger than this, we prefer to use the divided dose technic, using 1,000 r at each treatment, for three treatments. In about ten days following this type of radiation treatment there is moderate radiation reaction, with blistering and crusting of the skin, which

will persist for six to eight weeks, but, in our hands, with this type of treatment the skin usually heals well in eight weeks' time and leaves only a residual, thin, tissue paper-type of scar.

We believe that the irradiation treatment of small recurrent nodules of the skin is preferable to surgical removal, as surgery does not block surrounding lymphatics, and radiation treatment may be given without untoward reaction to the patients on numerous occasions. We have a number of patients, under observation at the present time, with scar metastases, who have been under treatment and followed for as long as three years without evidence of spread of the disease elsewhere.

USE OF ESTROGENIC SUBSTANCES FOR PALLIATION

Recently there has been much interest in the value of the treatment of advanced carcinoma of the breast by estrogenic substances, when these substances are given in relatively large doses.[5] In some cases this treatment has given remarkable relief of symptoms, such as pain, and has decreased the size of the tumor mass; occasionally, the ulceration has completely disappeared. This is contrary to our understanding of the growth of breast carcinoma, yet it is, in part, fundamentally sound because large quantities of estrogenic substances completely block pituitary secretion of follicular stimulating hormones, commonly known as FSH. Once the pituitary hormones are blocked off, healing of the tumor takes place temporarily but it is only occasionally that relief may be obtained by this method for over a year. There are some observers who feel that carcinomas of the breast become more radio-sensitive during this period that the estrogenic substances are being given.

There is another group of scientists who are giving testosterone propionate to the female in the hope of bringing about relief of symptoms. Again, this may be successful in some cases but in our hands it has not given favorable results.

About a year and a half ago a man, age 60, was admitted to the Clinic following radical mastectomy, with numerous bone metastases. He was given 30 mg. of estrogenic substances daily in the form of stilbestrol, with complete relief of pain and with gradual but complete healing of the bone lesion. Figure 2 shows the bone at the time administration of estrogenic substances was started, and Figure 3 shows the condition of the bone seven months following stilbestrol treatment. In eight months there was a gradual return of symptoms and further treatment by estrogenic substances did not give relief.

PALLIATION BY ROENTGEN STERILIZATION

In 1929, Dresser[4] reported on the value of roentgen sterilization in the treatment of bony metastases, and presented a case in which treatment had been given three years previously by radiation sterilization, with resultant healing of the bony lesions. This result lasted for a period of seven years. Since that time there have been numerous patients who have received roentgen sterilization in the younger group, who had obtained remarkable relief of pain

and an increase in their number of useful years. There have been more patients treated who did not improve following sterilization than did. In these

FIG. 2

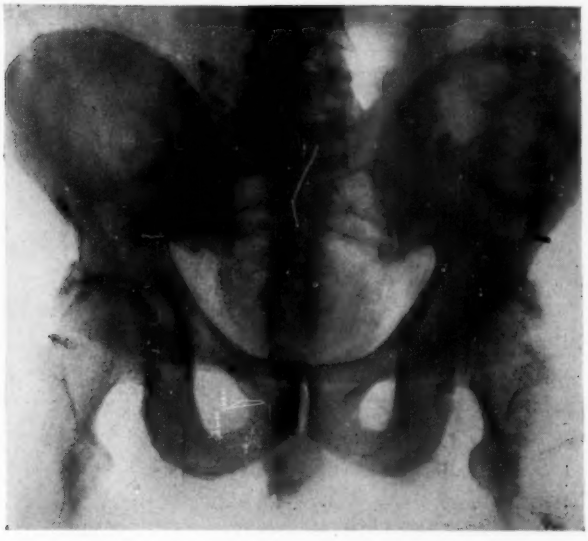

FIG. 3

FIG. 2.—Carcinoma of breast, male. Osteolytic metastases, particularly ischium on left (April 16, 1945).

FIG. 3.—Same case as shown in Figure 2, seven months later, showing repair, with disappearance of ischial lesion.

we add another problem which the patient had to solve; namely, the menopause, which comes at a time when she is mentally upset as a result of the tumor, a complication which has been very difficult to handle in several

instances. It was, therefore, deemed necessary to attempt to analyze the histories of those who did not receive benefit from radiation sterilization, likewise, the histories of those who did receive benefit from sterilization. It became apparent on reviewing these histories, and it has been reported by Sosman,[14] that radiation sterilization was successful only in those cases in which the pain in the metastatic region was increased, and there was associated pain and swelling of the opposite breast at the time of the menstrual period. If these be used as fair criteria for stopping the menstrual period, then a high percentage of patients will receive fair palliation (Figs. 4 and 5).

TABLE I

CARCINOMA OF THE BREAST — MORTALITY, UNITED STATES BUREAU OF VITAL STATISTICS

	No. of Deaths	Rate per 100,000
1942	15,954	11.9
1943	16,140	12.0

TABLE II

COMBINED THERAPY, RADICAL MASTECTOMY PLUS POSTOPERATIVE ROENTGEN THERAPY FIVE-YEAR SURVIVAL RATE—238 PATIENTS

	Number of Patients	5-year Survivals with No Recurrent Tumor	
		Number	Per Cent
No axillary node metastases at operation	94	71	75
With axillary node metastases at operation	144	53	37
Total	238	124	52.1

Adair, *et al.*,[2] found that roentgen-rays and surgical castration gives improvement in approximately 13 to 15 per cent, and that improvement is temporary and growth is retarded for about two years.

It has been our experience in the treatment of metastatic malignancy secondary to carcinoma of the breast that the patient is usually hopeful until the very end, is remarkably coöperative, and is usually willing to try any type of treatment suggested. It is important, therefore, that we should not give these patients any type of treatment which will make them more uncomfortable.

Each one of these patients in this study has been seen and examined by one or both of the authors in this follow-up, and we believe these statistics are as accurate as can be obtained by direct observation. Of this group of 238 patients who received the complete treatment, 52.1 per cent have survived five years or longer without evidence of recurrence (Table II). When this figure of 52.1 per cent five-year survival is contrasted with our previous experience of 38.6 per cent five-year survival after operation alone, it is evident that there is considerable improvement in the results of treatment, and we believe this must be attributed in a large measure to the added effect of roentgen therapy, as there has been no attempt to select for the combined treatment a group of cases which might offer a more favorable prognosis.

This is demonstrated by the fact that in this group of 238 patients, 62 per cent had metastases to axillary nodes at the time of operation (Table III).

Adair,[1] also, has stated that modern irradiation by the divided dose method

FIG. 4

FIG. 5

FIG. 4.—Roentgenogram taken October 6, 1944, showing multiple osteolytic metastases.

FIG. 5.—Same case as shown in Figure 4, two months later, showing healing of metastatic lesions.

after radical mastectomy has definitely increased the survival rate in his cases of cancer of the breast. His figures very closely parallel our experience in this regard; in his series, of 277 patients treated by radical mastectomy followed

by irradiation, the five-year survival rate was 76.8 per cent when lymph nodes were not involved and 41.8 per cent when axillary involvement was present (65.7 per cent of his group had axillary involvement). Adair has employed 1,800 to 2,250 r per portal. Harrington,[7] of the Mayo Clinic, also reported that the five-year survival rate in a large group of cases, with and without axillary involvement, was improved approximately 5 per cent by the addition of irradiation (Table III).

On the other hand, Haagensen, in reporting the results obtained in a series from the Presbyterian Hospital (640 with radical mastectomy), said that irradiation has not been of demonstrable value in his series. He reported a five-year clinical cure of 36.8 per cent after radical mastectomy alone, and 35.1 per cent when irradiation was used after operation. The roentgen dosage

TABLE III

RADICAL OPERATION WITH POSTOPERATIVE IRRADIATION
FIVE-YEAR SURVIVAL RATE

	Memorial Hospital Per Cent	Mayo Clinic Per Cent	Lahey Clinic Per Cent
Axilla negative:			
With roentgen therapy	76.8	75.4	75.0
Without roentgen therapy		70.2	
Axilla metastases:			
With roentgen therapy	41.8	29.4	37.0
Without roentgen therapy		24.3	

employed in this group, however, was considerably smaller than that employed by Adair, or the dosage used in our series, only 800 r per portal in three areas being used. McGraw,[10] in 412 cases from the Henry Ford Hospital, reported a five-year survival rate of 29.6 per cent in 251 patients with axillary involvement, and 64 per cent in 161 patients with negative axillary nodes. He stated that irradiation therapy was used in those patients with axillary metastases. Of 177 patients surviving five years, or longer, 116 were given deep radiation therapy, with 55 per cent having no evidence of recurrent tumor; of 61 not given radiation treatment, 59 per cent are living, and well, without recurrent tumor. He does not state the irradiation dosage used. On the other hand, some very capable observers feel that postoperative irradiation therapy is of doubtful value. Cantril and Buschke[3] believe that radiation treatment can slow up growth locally but will have no effect upon the ultimate progress of the disease. They believe that the greatest palliative accomplishment of roentgen therapy is retardation of bone metastases and alleviation of pain. This opinion seems at variance with our results since there appears to be quite definite improvement in our five-year survival rate as well as a decrease in the frequency of local recurrences.

LOCATION OF METASTASES

In studying our group of 238 cases which have been followed by us for over five years, it seems pertinent to analyze the cause of our failures and to study the location of the metastatic nodules, whether the recurrence took place as a result of lymphatic or hematogenous spread. It is quite apparent from our studies that the most common type of spread is through the lymphatics and, yet, once the original lymphatic area is treated by radiation, there is only small likelihood of recurrence or persistence in the area treated.

In this series a total of 114 recurrences was noted in different individuals. Their location is listed in Table IV.

TABLE IV

LOCATION OF RECURRENT MALIGNANCY—238 PATIENTS

	Lahey Clinic		Presbyterian Hospital
	Cases	Per Cent	Per Cent
Spread to opposite breast	8	3.3	9.1
Spread to bone	23	9.7	17.8
Generalized spread to bone and lymph nodes	25	10.5	
Recurrence in scar	14	5.9	
Recurrence in supraclavicular region	4	1.7	13.9
Recurrence in axilla	1	0.4	6.6
Recurrence in lung	24	10.0	21.6
Recurrence in abdomen and liver	7	2.9	9.8
Recurrence in cranium	8	3.3	

This shows that a total of 8 per cent of the cases had recurrence of their lesions in the scar area, supraclavicular, and axillary regions, and in this group of cases, 62 per cent showed signs of secondary malignancy to the axilla at the time of operation. This is, indeed, a small group as compared with the recurrences in this area usually noted. It seems necessary, therefore, to treat the scar, supraclavicular and axillary regions following operation especially in those cases in which there is evidence of secondary nodular disease at the time of operation.

Haagensen and Stout[6] report local recurrence in 22.8 per cent within five years in the operative field on the chest wall and in the homolateral axilla, whereas, with the combined treatment of surgery and radiation we found recurrent tumor in only 8 per cent, which figure includes the supraclavicular region as well. This lack of local skin recurrence appears most significant in our cases especially, in view of the fact that we have been more conservative in the removal of skin over the breast and chest area, in order, as stated before, that primary closure could be done and radiation treatment started immediately after operation. Certainly, it is evident by this conservatism that the frequency of local recurrent growths has not increased, as might be expected from other reports in which wider skin removal was thought absolutely necessary. Lewis and Rienhoff,[9] in a report from the Johns Hopkins

series, reported local recurrences after Thiersch graft to be 30.1 per cent; after closed plastic to be 39.7 per cent. White[15] is of the opinion that a chest without skin graft is preferable to one with a skin graft and that there is insufficient proof that the Halsted method of wide skin removal with Thiersch graft lowers the incidence of local recurrence as compared to the plastic skin closure of Handley.

Hoopes and McGraw[8] reported local recurrence to axillary and breast areas in 20 patients out of a total of 91 (22 per cent) upon whom skin graft was done, whereas, in 139 patients with plastic closure there were 22 with recurrence in these areas, an incidence of 16 per cent.

TABLE V

RESULTS OF RADICAL MASTECTOMY AND RADIATION TREATMENT
238 PATIENTS

		5 yr. Survival without Recurrence		Dead within 5 Years		Died within 2 Years after Operation	
	Cases	Number	Per Cent	Number	Per Cent	Number	Per Cent
Negative axilla	94	71	75.0	23	25.0	10	43.5
Axilla nodes positive	144	53	37.0	91	63.0	47	52.0
Total	238	124	52.1				

It is also significant to note that a large number of deaths took place within the first two years following treatment. Fifty-seven patients died in the first two years (Table V). This figure represents exactly 50 per cent of the total number dead (114) at the end of the five-year period: ten patients without axillary involvement at the time of operation and 47 patients with positive nodes were dead in the first two years. We could draw no conclusion concerning fertility relative to the combined therapy, yet it is significant, as to the occurrence of the disease at least, that cancer occurred in nulliparous women in 40 per cent of this group. Nathanson[11] stated that it is an accepted fact that nulliparous women have a relatively higher incidence of cancer of the breast than those who have borne children, and this high incidence of cancer in nulliparous women in this group is indicative of this fact.

The study in relation to age-groups, likewise, offered no significant data; there were only 28 patients of this group of 238 with the complete treatment who were below the age of 40, and we are unable to say whether the usually reported high early mortality after treatment is at all altered in young women by postoperative radiation or not (Table VI).

The largest group, 189 patients (80 per cent) ranged in age from 41 to 70 years. We did not hesitate to employ radical mastectomy in the older-age group, as indicated by the fact that there were 21 radical mastectomies in patients over 70, and yet in this entire group of 238 patients who had the complete treatment there was but one immediate death following treatment, an operative mortality of 0.42 per cent.

It is difficult in a series as small as the group reported in this paper to draw final and definite conclusions regarding this most important phase of recurrent malignant disease in breast cancer, but it does appear that immediate postoperative radiation therapy, given in adequate dosage, might well influence the occurrence of local recurrent growths, and reduce such local recurrences as well as improve the five-year survival rate. In any case, it is our opinion that there has been improvement in results of treatment of breast cancer by this method and that further information will need to be collected on a larger group of patients treated in a similar manner. We are continuing this method of treatment in the Lahey Clinic and at present have under observation a somewhat larger group of patients who have also had this type of treatment, beginning after 1942. The five-year survival rate is purely a

TABLE VI

AGE INCIDENCE—238 CASES

TREATMENT—RADICAL SURGERY PLUS POSTOPERATIVE IRRADIATION

Age, Years	Cases	
20–30	6	28 (11.7%)
31–40	22	
41–50	79	189 (80%)
51–60	66	
61–70	44	
71–80	21	

method of measurement of results of treatment and is not the ultimate or final result in any of these cases. What the results of a long range study may be can be estimated only after many years and perhaps after the majority of patients so treated may have died either from recurrent malignant disease or from other causes.

SUMMARY

Radical surgical removal of breast carcinoma followed by intensive irradiation treatment appears to improve statistical results in cancer of the breast and offers the best possibility for prolongation of life. In a series of 238 patients who received this type of treatment, 52 per cent were alive after five years, or longer, without evidence of recurrent tumor.

The incidence of local recurrent tumors is materially reduced, there being only 8 per cent of such recurrences noted in this series.

Radiation therapy, given in large amounts by the divided dose method, has produced no serious complications.

We believe that failure in treatment in many cases results from spread of disease to distant areas prior to institution of treatment.

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TREATMENT OF CANCER OF THE BREAST IN PREMENOPAUSAL PATIENTS WITH RADICAL AMPUTATION AND BILATERAL OOPHORECTOMY*

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THAT THE OUTLOOK for cure of carcinoma of the breast is more discouraging in young women than in those in the postmenopausal period has been rather generally accepted. Sittenfield[1] states: "Every cancer worker realizes that cancer of the breast in a woman under 40 years of age is a highly malignant disease and notwithstanding the most thorough surgical excision and large doses of radiant energy, the end-results are very grave and disappointing." Ewing[2] has stated: "Before 30 years of age mammary cancer is extremely fatal, so that some surgeons prefer not to operate during this period."

The relationship of the endocrines to certain types of cancer seems to be definitely established. When, in 1932, Lacassagne[3] induced mammary carcinoma in male mice by injections of estrone benzoate it was apparent that an important step forward had been made in the understanding of the causes of mammary cancer. This led to a variety of interesting findings concerning the general effects of the estrogens on neoplasms. Likewise, Huggins[4] and his coworkers have established in their experimental and clinical work on cancer of the prostate a definite relationship with male sex hormone. Whatever may be the explanation of the benefits of orchiectomy on cancer of the prostate, and they certainly exist in many cases, it would seem that an analogy might apply to bilateral oophorectomy in cancer of the mammary gland.

Shimkin[5] states: "It was found that mammary tumors occurred more frequently in breeding than in nonbreeding mice. In some strains, the incidence of tumors is proportional to the number of pregnancies undergone by the mice. Loeb[6] further demonstrated that the incidence of tumors can be radically reduced by ovariectomy, and that the incidence is related to the age of the animal at the time of ovariectomy. Cori,[7] and W. S. Murray,[8] substantiated these findings, and the latter succeeded in obtaining mammary tumors in castrated male mice bearing ovarian grafts."

"With the advent of chemically isolated estrogens, numerous investigators reported the appearance of mammary tumors in male mice injected with these compounds. The work was rapidly expanded and elaborated. The most important conclusion was that estrogens would elicit mammary tumors in males of strains in which females developed such tumors spontaneously, and in approximately the same incidence. Males of strains in which the tumor incidence was

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extremely low did not develop a mammary cancer no matter how strenuously they were treated with estrogens. This would indicate that the strains known to be readily susceptible to cancer of the breast, whether male or female, would develop cancer of the breast by injections of estrogens."

Mammary carcinoma in male mice of susceptible strains has been developed with all the natural and synthetic estrogenic compounds that have been studied. The list includes estradine, estrone, estriol, quilenin and their benzoates, diethylstilbestrol, *etc.* The carcinogenic activity of these substances seemed to be related to the amount of estrogen in physiologic units rather than to chemical structure or other properties of the substance injected. They could be administered subcutaneously, intramuscularly, or orally with the same results, depending on the physiologic activity by the particular route employed. The administration had to be continued for a prolonged period, eight weeks or more, if carcinoma was to be developed at a later period. Compounds having rapid elimination and consequently a shorter period of activity had to be given in larger doses and administered over a longer period than those compounds given as subcutaneously implanted pellets.

The site, the growth, and the histologic appearance of the mammary tumors developed in castrated mice injected with estrogens correspond in every detail with the description of the spontaneous adenocarcinomas in female mice of the same strain.

Using rats of the Long-Evans hooded strain, in which only four fibroadenomas had been seen in 15 years, Nelson[9] reported the induction of 68 carcinomas of the breast in 103 animals. He gave daily injections of 50 *gamma* of diethylstilbestrol, or subcutaneously implanted pellets of diethylstilbestrol. Metastases developed in 33 rats, which were classified as: duct carcinoma, 13; adenocarcinoma, 8; duct and adenocarcinoma, 13; and carcinoma simplex, 5. He found that both male and female rats were equally susceptible to the induction of tumors. Numerous other workers have repeated the experiments, using the same strain of rats, with essentially the same results.

Geschickter[10] injected a number of castrated rabbits with daily doses of 0.5 or 1.0 mg. of dimethylstilbestrol. Three rabbits developed papillary cystadenoma of the breast in 10 to 15 months, and in one this progressed to carcinoma within 20 months.

In earlier investigations by Loeb[11] it was shown that there is a direct quantitative relationship between the duration of the action of endogenous ovarian hormones and the incidence of carcinoma of the mammary gland in mice; the longer the endogenous hormones were allowed to act, the greater the incidence of carcinoma. It was also shown by Lathrop and Loeb[12] that the latent period preceding the appearance of carcinoma of the mammary gland was in a similar way related to the duration of the action of the endogenous hormones; the longer the endogenous hormones were allowed to act, the shorter the latent period.

It follows from their earlier experiments that removal of the action of

ovarian hormones at a period of life when the mice had passed the onset of sexual maturity was effective in diminishing the incidence of mammary carcinoma and in increasing the latent period.

Shimkin further states: "It is abundantly clear that in all species, carcinoma of the mammary gland is the end-result of an intricate, prolonged interaction and combination of at least several factors or complexes of factors. In all species, a degree of genetic susceptibility and a degree of hormonal stimulation are essential, and the process can be modified by numerous secondary influences of internal and external environment."

What seems to be the double rôle of estrin in the causal and in the formal genesis of mammary cancer resembles what might be the relationship between androgenic substances from the testicle and cancer of the prostate. The beneficial results of removing the ovaries along with a radical operation for cancer of the breast may be attributed to the withdrawal of a causal genesis, to the removal of a formal genesis, or to a combination of both of these factors. The recurrences of cancer of the breast after a radical operation are doubtless due to cancer cells that have been left. The small amount that remains, however, would be stimulated by estrogenic substances. As there have been cases in which cancer of the breast receded, at least temporarily, after removal of the ovaries, with no other treatment, it would seem that there may be a mass relationship. That is, the effect of withdrawing estrogenic stimuli might be greater if there are only a few cancer cells than if there is a large amount. With only a few remaining cancer cells, however, this unfavorable influence of withdrawing the stimulating effect of estrin should be more deleterious and create an unfavorable soil for their existence.

In women who have previously had cancer in one breast, the increase of ovarian activity in pregnancy appears to promote mammary cancer in the remaining breast. Trout[13] collected 15 instances of pregnancy subsequent to a radical operation for mammary cancer, in 13 of which there was prompt development of very malignant carcinoma in the remaining breast. Wintz[14] reported seven instances of pregnancy after radical operation for mammary cancer, with fatal cancer then occurring in the remaining breast.

Ultimate results from the treatment of cancer of the breast in young women were most disappointing. J. Shelton Horsley found this to be true in his cases prior to 1937. Of nine patients under 36 years of age upon whom a radical operation was performed by him at St. Elizabeth's Hospital in the period from September 1, 1922 to November 1, 1937, five died of recurrence. The marked difference in the results obtained in this younger age-group, as compared with those in older patients, and the results of experimental work already referred to, caused J. Shelton Horsley[15] to adopt the procedure of removing both ovaries whenever a radical operation is done for cancer of the breast in women in the premenopausal period.

Four years after he did the first bilateral oophorectomy associated with radical amputation of the breast, which was on November 19, 1937, the splendid report of Huggins on castration for cancer of the prostate appeared. His

work seems to confirm the wisdom of bilateral oophorectomy in premenopausal women whenever a radical operation is done for cancer of the breast. This procedure apparently was first suggested by Schinzinger,[16] although according to his article, he did not carry it out. He is said to have discussed this also before the Surgical Congress in Berlin on April 25, 1899. Doubtless, it has been performed by other surgeons, although there does not seem to be any systematic record of a number of cases.

At first a bilateral oophorectomy was done with radical operation for cancer of the breast only on patients under 40 years of age. Later, this was extended to all patients in the premenopausal stage. The desirability of having both ovaries removed along with the radical operation is, of course, first explained to the patient.

Since beginning this method of treating cancer of the breast, numerous investigators have reported excellent results by roentgenologic or surgical castration in patients with extensive carcinoma in both the pre- and postmenopausal periods. Ritvo and Peterson[17] reported definite regression of osseous metastases from carcinoma of the breast following ovarian sterilization by roentgenologic treatment. With regression of the metastases there was also marked relief of pain, which was quite similar to the relief of pain in patients with osseous metastases from carcinoma of the prostate.

Treves, *et al.*[18] reported regression of a primary lesion in two cases following bilateral oophorectomy and improvement in another case. They also noted clinical regression in metastases in both the lung and bone, and in several cases there was dramatic relief of pain immediately following castration. Recently, Adair and Herrmann[19] have reported using large amounts of testosterone propionate in treatment of advanced carcinoma of the breast. They reported 11 cases treated, with improvement in four cases associated with relief of pain; no improvement in four cases; and three cases were still under treatment when their report was made. Three of the four cases reported in detail were in their fourth decade, and all of them seemed to show improvement, with a sense of well-being, definite gain in weight, and clinical and roentgenologic evidence of regression of the neoplasms. Two of these three cases were menstruating when the injections of testosterone were started, and after injections developed amenorrhea.

J. Shelton Horsley presented the results up to November 1, 1943, of his cases of radical amputation of the breast with bilateral oophorectomy. A further report on this work is given in the following Tables. In addition to the results obtained on patients in the premenopausal stage, Table I shows results from all cases of cancer of the breast admitted to St. Elizabeth's Hospital between November 1, 1937 and November 1, 1946. These statistics are shown so that the comparison in the different age-groups may be noted.

In Table I there is a total of 170 cases, showing living and no recurrence 108, living with recurrence four, and 54 deaths. Of the dead, 36 were from recurrence, 11 from causes unknown—some of which undoubtedly were from metastases, and seven from causes other than metastases.

Table II includes only those cases without oophorectomy, but five of these cases had sterilization by roentgen-ray. There is a total of 131 cases, with no recurrence in 78; living, with local recurrence three. Total deaths were 46, of which 29 were definitely from recurrence; 11 from causes unknown; and six from causes other than metastases.

TABLE I

CANCER OF BREAST

All cases admitted to St. Elizabeth's Hospital, Richmond, Virginia between November 1, 1937 and November 1, 1946

Total cases		170
No recurrence		108 (63.5%)
Recurrence and living		4 (2.4%)
Dead:		54 (31.7%)
From recurrence	36 (21.2%)	
Causes other than metastases	7 (4.1%)	
Cause unknown	11 (6.4%)	
Follow-up incomplete		4 (2.4%)

TABLE II

CANCER OF THE BREAST WITHOUT OOPHORECTOMY

November 1, 1937 to November 1, 1946

All cases without oophorectomy		131
No recurrence		78 (59.5%)
Recurrence and living		3 (2.3%)
Dead:		46 (35.1%)
From recurrence	29 (22.1%)	
Causes other than metastases	6 (4.6%)	
Cause unknown	11 (8.4%)	
Follow-up incomplete		4 (3.1%)

TABLE III

CANCER OF THE BREAST WITHOUT OOPHORECTOMY

November 1, 1937 to November 1, 1946

Cases traced		127
No recurrence:		78 (61.4%)
Oldest patient—77 years of age		
Youngest patient—28 years of age		
Under 35 years of age—2		
Under 40 years of age—5		
Recurrence and living:		3 (2.4%)
Local, after 3 years—1 age 49		
Local, after 2 years—1 age 66		
Local, after 5 years—1 age 35		
Dead:		
From recurrence	29 (22.9%)	46 (36.2%)
Causes other than metastases	6 (4.7%)	
Cause unknown	11 (8.6%)	

Table II is further broken down into Table III, and it will be noted that in patients without recurrence there were several still in the premenopausal stage—two under 35 years of age and five under 40 years of age. Of these five, none had roentgen-ray treatment over the ovaries for one reason or

another, the chief one being a low-grade type of malignancy with either an intraductal or mucoid type in which sterilization seems to be of less value. There are three cases living, with local recurrence, one of whom was in the premenopausal stage at the time of operation and was sterilized by roentgen-ray. However, six months after the first roentgen-ray sterilization, she began menstruating and had to receive roentgen-ray therapy over the ovaries on two other occasions before a complete and final suppression of menstruation was effected. All three recurrence and living cases have had local excision of the recurrent nodules, and recent examinations showed no evidence of further trouble.

Of the 29 deaths from known recurrence, eight cases were in the premenopausal period. One case, age 34, was so extensive that only a diagnostic biopsy was done; three other cases had only the radical operation, and all died within two years. The remaining four cases had roentgen-ray sterilization in addition to the radical operation. Of these four cases, one died after two years, one after four, one after five, and one after nine years. It was because of incomplete castration by roentgen-ray, two of them requiring further roentgen-ray treatment over the ovaries six months later, that it was decided surgical sterilization was the procedure of choice when castration was indicated, with radical amputation of the breast for cancer.

TABLE IV

RESULTS THREE AND FIVE YEARS AFTER OPERATION IN CASES WITHOUT OOPHORECTOMY

	Operated Upon 3, or more, Years		Operated Upon 5, or more, Years	
Total cases	97		62	
Living:	55 (56.6%)		28 (45.1%)	
No recurrence	53 (45.6%)		27 (43.5%)	
Local recurrence	2 (2.0%)		1 (1.6%)	
Dead:	42 (43.3%)		34 (54.8%)	
From recurrence	28 (28.8%)		23 (37.1%)	
Causes other than metastases	4 (4.2%)		4 (6.4%)	
Cause unknown	10 (10.3%)		7 (11.3%)	

Realizing that many of these cases have been of recent origin, and a true index of cures is not given in the preceding Tables, the recent cases were eliminated. Table IV gives the results of those without oophorectomy operated upon three years, or more, and five years, or more. There is a total of 62 that have been operated upon five years, or more, of which 28, or 45.1 per cent, are still living. One of these—the patient who had roentgen-ray castration, as mentioned in Table IV—has a local recurrence. There are 34, or 54.8 per cent, dead. Of this number, 23, or 37 per cent, died from recurrence; seven, or 11 per cent, from causes undetermined; and four, or 6 per cent, from causes other than recurrence. Assuming that all of the deaths whose exact cause is not known were from recurrence, there would be a total of 30 deaths, or only 48.4 per cent. Of the patients operated upon three, or more, years ago, which include the cases operated upon five years ago, or more, there is a total of 97; 55, or 56.6 per cent, of whom are still living. Two of these have had

local recurrence, but at present there is no evidence of any further metastasis. Of these 97, 42, or 43.3 per cent, have died—28 from recurrence, ten from causes undetermined, and four from causes other than recurrence.

TABLE V

CANCER OF BREAST WITH OOPHORECTOMY

November 1, 1937 to November 1, 1946

All cases with bilateral oophorectomy		39
Living:		31 (79.5%)
No recurrence:	30 (76.9%)	
Oldest patient—50 years of age		
Youngest patient—28 years of age		
Average age—40.6 years		
Under 35 years of age—4		
Under 40 years of age—14		
Recurrence:		
Local, after 4.5 years—age 43	1 (2.5%)	
Dead:		8 (20.5%)
From recurrence:	7 (18.0%)	
After 6 months—1 age 28, bilateral, with metastases to axillae at time of operation		
After 1 year—1 age 38, metastasis to bone		
1 age 38, local metastasis		
1 age 44, extensive axillary involvement at time of operation		
After 2 years—1 age 43, metastasis to lung		
After 3 years—1 age 33, metastasis to bone		
After 5 years—1 age 38, metastasis to lung		
From causes other than recurrence	1 (2.5%)	
Age 30, from peritonitis 5 years after operation. Autopsy showed no recurrence		

Table V includes all cases in which bilateral oophorectomy was done at the time of operation, with a total of 39. There have been no recurrences in 30; local recurrence in one; and eight deaths, seven of which were from recurrence and one from causes other than metastasis. The oldest of the living patients was 50 and the youngest 28 at the time of operation. The average age was 40.6 years. There were four under 35 years of age and 14 under 40 years of age. There is one living who has had a local recurrence, the original operation having been done 4.5 years ago, when she was 43 years of age. She has had several recurrences in the skin, occurring at about yearly intervals, the last one being a little over a month ago. The patient at present seems to be in excellent condition, and there is no indication of other metastases. There were eight deaths in the series, seven of which were from definite recurrence and one from general peritonitis following intestinal obstruction five years after the original operation. Necropsy in this case revealed no evidence of recurrence of the malignancy. One case, 28 years old at the time of operation, who had extensive cancer of both breasts, with metastases in both axillae, died six months after operation. The other six cases died of metastasis—three, one year after operation; one, two years after operation; one, three years after operation; and one, five years after operation.

Table VI shows cases three and five years after the original operation, with bilateral oophorectomy. Thirteen cases were operated upon five years ago, or more, and of these, ten are living without recurrence, and one had local skin

recurrence. This gives a percentage of 76.9 living without recurrence after five years. There is a total of 26 that were operated upon three or more years ago, with one local recurrence, as shown in the five-year cases. There were five deaths from recurrence, giving 76.9 per cent of three-year cures, which is the same as that noted in the five-year, or more, cases.

TABLE VI

RESULTS THREE AND FIVE YEARS AFTER OPERATION IN CASES WITH OOPHORECTOMY

	Operated Upon 3 or more Years	Operated Upon 5 or more Years
Total cases	26	13
No recurrence	20 (76.9%)	10 (76.9%)
Local recurrence	1 (3.8%)	1 (7.7%)
Dead from recurrence	5 (19.3%)	2 (15.4%)

While this paper is primarily concerned with the results obtained in cancer of the breast cases in the premenopausal stage treated by radical amputation and oophorectomy, we have reviewed in some detail the results obtained in all cases of cancer of the breast admitted to St. Elizabeth's Hospital during this nine-year period. This is done so that the results in those cases without oophorectomy, and mostly in the postmenopausal period, may be compared with those in the premenopausal period, with oophorectomy. This comparison should be significant, as it covers the same period of time, all operations were done by one of three surgeons, and the same operative procedure was used. It will be noted in the five-year "cures" that there were 43.5 per cent in those cases without oophorectomy as compared with 76.9 per cent in those of the premenopausal period with oophorectomy. The same results were observed in the three-year cases in the latter group.

This series of cases, combining bilateral oophorectomy with radical amputation of the breast, is too small to be conclusive, but, in our hands, the results have been outstanding, considering the discouraging reports before oophorectomy was done with the radical amputation. The results are much better than those obtained when roentgen-ray castration was tried, though our few cases treated with roentgen-ray were better than those without either method.

There might be further improvement by the administration of testosterone propionate even after oophorectomy. The recent reports of Adair and Herrmann show that fair results are also obtained by such injections in elderly patients past the menopause with extensive metastases. We have not yet tried these injections either with or without oophorectomy. There have been several reports on the use of testosterone propionate injections without oophorectomy with good results, but as this would be a prolonged procedure it would seem that oophorectomy would be more certain and less hazardous. The objection to the use of the male hormone is quite similar to that of roentgen-ray castration. In some patients sterilization is not complete and the size of the injection or radiation often has to be increased before the desired results are obtained. It is this delay and uncertainty in effecting complete suppression of the female hormone that makes these methods unsatisfactory. Numerous other

factors are involved in the development of breast cancer, such as heredity, the milk factor, *etc.*, as have been shown in experimental and clinical research, but surgical castration of those patients in the premenopausal stage with radical amputation of the breast is a step forward in the right direction.

SUMMARY

1. A brief review of the recent literature on the influence of female hormone on breast cancer has been given.

2. Results obtained by radical amputation of the breast and bilateral oophorectomy in cancer of the breast in premenopausal cases are given, showing 76.9 per cent of cases living without recurrence in both three- and five-year postoperative periods.

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DISCUSSION.—DR. EDWIN P. LEHMAN, Charlottesville, Va.: My remarks are directed only to Doctor Horsley's paper. The general principle underlying the approach to the treatment of possibly curable malignant disease is the destruction of the disease, no matter what anatomic or functional loss is entailed, short of death or degrees of crippling which are worse than the effects of cancer. This principle must be applied in borderline instances with considerable caution. In specific instances it must be finally accepted only when there is proven evidence of effectiveness of the treatment.

In applying this principle to the problem of castration of women with cancer of the breast, we must appraise both the harmful effects of castration and the effectiveness of the procedure. It is, of course, well known that a premature menopause in many women is a serious psychic hazard. In other women, particularly those who have already had children, it may be welcome. I agree with Doctor Horsley that women who have had cancer of the breast should never again become pregnant. Certain women would decidedly prefer castration to the deformity of a radical amputation of the breast, which we do not hesitate to employ without concern about the psychic effects. It is obvious, therefore, that no generalization with regard to the desirability or undesirability of castration will cover all women. If castration is to be employed, it must be used with judgment and particularly with due consideration to the expected psychic result in the individual case. It is undesirable, but so is radical mastectomy. If it has a favorable effect on the cure rate of cancer of the breast in young women, there are certainly many instances in which it can be applied without fear of serious psychic crippling.

The determination of its effect on the prognosis of mammary cancer is not easy. Its application is based, of course, on the well-established endocrine relationships of cancer of the breast in the animal, as outlined by Doctor Horsley. Certain isolated instances of an analogous effect in the human being are on record.

It is natural, of course, that even a single experience of an unmistakably favorable effect will influence the approach of any clinic to this problem. At the University of Virginia Hospital we have under observation a case of eight-year cure without surgical operation. A young woman of 30 with widespread mammary cancer, proven by biopsy from a huge mass in the ipsolateral supraclavicular space, was castrated by roentgen-ray in 1938. This was the only primary treatment. Every visible evidence of tumor disappeared. One year later local roentgen-ray treatment was given. This patient, in 1946, is alive and well, without evidence of disease in the breast itself or in local or distant metastatic areas. Whether or not the local roentgen-ray therapy given in 1939 had an influence on the eight-year cure is not pertinent to the present discussion, since huge masses of tumor disappeared within a short time after castration had been completed. It was this case which led us to carry out castration in certain cases of premenopausal cancer. We have not employed it in all cases but have reserved it for instances in which psychic disturbance was not feared, or in cases presenting inoperable metastases, such as the case cited. During the earlier years castration was done by roentgen-ray. Just as Doctor Horsley has reported, several cases began to menstruate after supposed roentgen-ray castration, and we, therefore, adopted oophorectomy in 1942.

In attempting to appraise results it seems to me that the material must be separated into two groups: namely, castration at the time of radical operation and palliative castration in advanced cases after metastasis has occurred. The former may be called primary castration and the latter secondary. Of the former group we have had 20 cases in which cancer was proven; of the latter, six cases including the case already cited. It is impossible, of course, with only 20 cases over a period of eight years, to measure the results of this procedure on the cure rate. There have been only six cases that were treated more than five years ago and nine cases more than four years ago. In these small subgroups the five-year cures parallel the absence of axillary metastasis.

It is easier to judge the effect of secondary castration, but only if no other therapy is employed. If castration is the only treatment, as in the case mentioned, and marked immediate improvement occurs in a proven tumor, the inference that the treatment is

responsible is fairly direct. In the advanced cases this improvement need not result in a five-year cure to be demonstrative. In our six cases of secondary castration there are only two cases in which castration was not accompanied immediately by other therapy. One of these is the case already reported. In the other there was marked early regression of the lesion without any local roentgen-ray treatment. Death occurred two years later.

Certainly, the experience in our clinic does not yet prove that castration is a justified adjuvant to radical mastectomy. It is our intention to continue to use the method conservatively, however, with the hope that within another five or ten years data will be available to demonstrate the presence or absence of a favorable effect.

Doctor Horsley's interesting paper evidences a similar approach. I wish, however, that he had presented comparisons between cure rates in premenopausal cancer with and without castration, correlated with the extent of disease as the time of treatment, especially as regards axillary involvement. This factor might prove to be more influential upon his excellent rate of five-year cures in a small series than the accompanying castration.

DR. HUGH H. TROUT, Roanoke, Va.: When one has been intensely interested in any subject for 35 years, or more, it is almost impossible not to discuss the subject when it comes up for discussion. However, in order that I may not wander over the face of the earth, I have made some notes so that I might limit my time. It is almost impossible to evaluate the effects of cancer education. In our series of more than 500 there have been 29 women who are the wives of doctors. The time this group allowed to elapse between the time they felt a lump in the breast and the time of reporting the same to their physician averaged nine months; with the women in the rest of the series, this average time was three months. I do not feel that doctors have selected unintelligent women for wives, but I do think the average patient is afraid of cancer and hesitates about reporting the same for fear of what she has heard about the hopelessness of cancer.

One factor has remained very constant over the years; we felt when we were under Doctor Halsted's influence, and later under Doctor Finney's, that the best hope for the cure of cancer was the radical extirpation of the disease *en masse*. That is the "sheet anchor" to which we tied all these years. At present, we are not using preoperative irradiation. Perhaps this is somewhat due to the horrible results of the so-called "Coutard" treatment, with its occasional case of skin necrosis. Frequently, with preoperative irradiation the lump in the breast decreased in size and the patient thought she was improving, and did not report for progress-checks until the growth had again increased in size, and occasionally the malignancy was then farther advanced than when first seen. We do use radiation in young women in rapidly growing malignancy, and particularly if associated with infection. We have felt in a few cases that with preoperative irradiation inoperable cases have been converted into operable cases.

One observation we have made is that if there are one or two large malignant nodes in the axilla, it is a better prognosis than where a chain of small hard shot-like nodes are found. We are still old fashioned enough to flush out the whole field of operation with very hot saline solution. We have the feeling that stray cancer cells, being of very low resistance to heat, might be killed by heat. In addition, the mechanical effects of washing out with large quantities of water might remove some loose cancer cells.

Another observation we have made over the years is that if a node is found under the triangular or falciform fascia which is under the pectoralis minor muscle, the prognosis is bad. Such a finding indicates that the malignancy has extended through the chest wall. Not one of these cases has lived longer than a year, in spite of the fact that no metastasis is shown by roentgenologic studies.

The use of radium at the time of operation we have found of advantage. Just before we close the flaps, we take two long rubber tubes containing radium. We put one of these tubes with radium in the axilla and the other in the region of the distribution of the internal mammary.

We have had something over 170 cases without a single local recurrence. However, this did not improve our five-year "cures" one bit. Eight or ten days after operation we start roentgen-ray treatments, using as many portals of entry as we can. If the skin flaps are not in good condition, such treatment must be postponed. On a recent visit to Boston, I was much interested in talking to the research men working with the one and two million volt machines. My own impression is that we have no reason to expect any improvement, at least at an early date, over the 250,000 volt machine. We do know that these extremely high voltage machines are capable of very wide destruction of both malignant and normal tissue.

In 1931, Peterson, our radiologist, was treating bone metastasis in the pelvis in young women. He was doing this for relief of pain. We were much surprised to see the improvement in the breast condition. The local improvement was truly remarkable. The patient died, but it was interesting that the breast improved by the establishment of the cessation of menstruation. Certainly, irradiation, if properly done, stops the menses and, thus prevents future pregnancy and future lactation. That was the beginning with us of the use of artificial menopause produced by irradiation for the control of malignancy of the breast.

In a recent letter from Frank Adair of New York, he said he had stopped the postoperative use of testosterone propionate except in cases of bone metastasis. We have had no experience with this except in two cases, and neither of these received relief.

I do not know how one can tell definitely what irradiation plus surgery is doing with these cases. I do know our five-year results over this large series of ours, where they have been taken "catch-as-catch-can" have improved since we have been combining irradiation (radium and roentgen-ray) with surgery. We had in a group before 1936, five-year "cures" of 41 per cent; the next five-year group, stopping in 1942, had "cures" of 57.6 per cent. We did not feel that we are seeing earlier cases or that our operative procedures have improved to such an extent as to explain this improvement in these two five-year studies, therefore, we conclude that irradiation has been of benefit in improving our surgical results.

Dr. Bradley L. Coley, New York City: We are very fortunate in having three papers dealing with the treatment of cancer of the breast along three accepted lines—surgery; surgery plus irradiation; and hormone therapy. Several aspects of breast cancer are of special interest to the surgeon who is particularly concerned with malignant conditions involving the skeletal system.

I would call attention to the fact that in certain cases the first symptom presented by the patient is referable to bone metastasis; the presence of the primary breast tumor has been wholly unsuspected until after the bone lesion has been demonstrated on roentgenologic examination, and a careful search discloses the primary lesion.

In women who have had radical mastectomy and who later (one to four, or more, years) have complained of backache or pain in a major long bone, the initial roentgenologic examination may be reported as negative. Repeat films are indicated if symptoms persist, and will often subsequently reveal osseous involvement.

The treatment of bone metastasis from breast cancer is wholly palliative. It may consist of (1) roentgen therapy to the affected areas; (2) roentgen or surgical castration; and (3) hormone therapy, using male sex hormone. We still lack sufficient knowledge, based on a large enough series of cases, to state that castration of the premenopausal women is best carried out by oophorectomy or by high voltage roentgen-ray therapy; I suspect surgical castration is more effective.

We know that a substantial proportion of cases of breast cancer, with skeletal metastases, have shown clinical and roentgenographic evidence of improvement following roentgen-ray castration. The clinical improvement has been found to be more striking than that shown roentgenographically, and it may persist for periods ranging from six

to 18 months, or longer. When metastases to nodes or to viscera are considered, the improvement has not been striking.

Testosterone propionate also benefits a substantial proportion of females with breast cancer metastases to bone. On the average, favorable response may persist for about six months, occasionally it lasts as long as 18 months. However, a word of caution is necessary, because a small proportion so treated are made much worse by the administration of male sex hormone owing to the severe hypercalcemia which is induced, so that this method is not without danger.

DR. STUART W. HARRINGTON, Rochester, Minn.: I congratulate the essayists on the splendid presentations that they have given on the results of surgical treatment for carcinoma of the breast. I am pleased that Doctor Finney has emphasized the importance of a thorough radical mastectomy in the treatment of carcinoma of the breast, as I believe this is a very important consideration in the end-results. I wish to compliment Doctor Marshall on the very comprehensive and thorough study he has made as well as on the excellent results he has had in the surgical treatment of carcinoma of the breast.

I have been interested for a number of years in the factors which influence the results of surgical treatment of carcinoma of the breast. Some of the more important factors are as follows: (1) the extent of the malignant involvement at the time of operation; (2) the thoroughness with which the radical operation is done; (3) the degree of malignancy as shown by microscopic examination of the primary lesion; (4) the presence of other associated conditions, such as pregnancy; (5) the general constitutional diseases, such as diabetes; and (6) the age of the patient.

There are unavoidable inaccuracies in statistical studies because of the difficulty in obtaining accurate classifications of cases due to the many factors that influence prognosis. Statistical studies of the results of treatment of mass-groups of patients are often misleading. This is particularly true when comparing the results obtained from different types of treatment; in these studies it is imperative that only similar groups of cases be used for comparison. I do not believe that comparative studies are of value unless it is definitely known that the groups compared are similar as to the type and extent of the disease.

Although axillary nodal metastasis is only one of the factors that may indicate the extent of the disease at the time of operation, I believe it is one of the most important factors indicating the prognosis following operation because of the great influence it has on the survival rates. Because of this fact, in compiling statistical studies of survival rates of malignant disease of the breast, I believe that all cases should be divided into two main groups—those with and those without axillary nodal metastasis at the time of operation.

The importance of the presence or absence of axillary nodal metastasis at the time of operation is shown in a study of 6,149 patients who had radical mastectomy in which 6.5 per cent had axillary nodal metastasis at the time of operation. The patients who did not have axillary nodal metastasis at the time of operation constitute 39.5 per cent of the entire series. The proportion of this group of patients living three years, or more, after operation was 85.0 per cent, or almost twice as large as that for the group with axillary metastasis, which was 45.3 per cent. In the five-, ten-, fifteen-, and twenty-year survival rates of patients without axillary nodal metastasis, it was found that the improvement increased progressively over the group with axillary metastasis. For the five-year period, the survival rate for the group without metastasis was 75.7 per cent, or two and one-half times as large as that for the group with metastasis, which was 30.4 per cent; for the ten-year period it was three and one-half times as large, or 57.9 per cent without metastasis, and 16.4 per cent with metastasis; for the fifteen-year period it was four times as large, or 44.4 per cent without metastasis and 11.1 per cent with metastasis; and for the twenty-year period it was more than five times as large, or 33.5 per cent without metastasis and 6.5 per cent with metastasis.

A quinquennial study was made of unilateral carcinoma of the breast in women who had had radical mastectomy from 1910 to 1938, inclusive. The last period is only four years (1935–1938) because patients operated upon in 1939 had not been operated upon for a sufficient length of time to enable five-year results to be compiled. This study was made up of 5,558 patients, of whom 5,407 were traced. The patients are divided into two groups, those with and those without axillary nodal metastasis at the time of operation. It was found that there was a consistent and appreciable improvement in the results obtained from radical mastectomy in each of the five-year periods. The study of patients presenting axillary nodal metastasis at the time of operation from 1910 to 1914, inclusive, shows that 23.7 per cent were living five years after operation as compared with 39.1 per cent of those upon whom operation was performed during 1935 to 1938, inclusive. In this study the results obtained in patients without nodal metastasis at the time of operation show a greater improvement, in that there was 62.7 per cent of five-year survivals from 1910 to 1914 as compared with 81.9 per cent from 1935 to 1938.

This improvement in the results of surgical treatment was present whether or not the patient had roentgen-ray treatment, and it indicates that the educational program in which the medical profession has participated for many years is becoming effectual in that we are seeing a higher percentage of patients without axillary nodal metastasis.

Dr. L. Wallace Frank, Louisville, Ky.: In a discussion of cancer of the breast at the meeting of this Association held at Augusta, Georgia, some years ago, I made the statement that I had observed very few cases of skin recurrence. Now I wish to retract that statement, for I have seen quite a number since then. The most remarkable instance of skin recurrence is under my care at the present time. In the Spring of 1926 a radical left mastectomy was performed for cancer of the breast. In the Spring of this year, 1946, she came in to see me on account of a red area in the epigastrium. This was indurated and slightly elevated. The lesion was excised and the specimen was sent to the laboratory. The pathologist made the diagnosis of adenocarcinoma of the breast, recurrent in the skin. So far as I know this is the longest interval between operation for cancer of the breast and skin recurrence.

From January 1st, 1937, to August 1st, 1946, I have performed 136 operations for breast cancer, in my private practice; these were undertaken on 133 patients. One patient developed cancer in the second breast 15 months after her first operation; in a second patient, cancer occurred in the remaining breast four and one-half years after the first operation; in a third instance, the cancer appeared in the remaining breast 18 months after the removal of one breast. This last patient falls into the group of so-called familial cancer. Her maternal grandmother, her mother, and an older sister died of breast cancer; her twin sister died at the age of 21 of the same disease.

Of these 133 patients 56 per cent had proven axillary metastasis at the time when first seen. This figure is comparable to that of Doctor Marshall's series. Such a high incidence of axillary involvement indicates two things: First, that regardless of the dissemination of knowledge of signs and symptoms of cancer among the laity, patients still do not come at an early stage of the disease. Second, and perhaps even more important, is that it demonstrates the fact that the family doctor should be educated to recognize early lesions of the breast. It is only by operating at an early stage of the disease that the curability (and I use this word advisedly) of breast cancer is to be increased.

Between January, 1937, and August, 1944, 105 patients were operated upon. Of the cases with no axillary involvement 80 per cent are alive and well; of those having axillary metastasis 50 per cent show no evidence of the disease.

Dr. J. Stewart Rodman, Philadelphia, Pa.: Adequate skin removal has always been a very important factor in a radical breast amputation. Seventy years ago two very distinguished surgeons in Philadelphia were doing this operation. Samuel W. Gross was

doing an amputation by a large circular incision of the breast, and was curing 9.5 per cent of his cases. At the same time, Doctor Agnew, Professor of Surgery at the University of Pennsylvania, said he had removed a carload of breasts and never cured a case. He was removing the breast through a small elliptical incision which sacrificed very little skin. Ever since that time wide removal of skin has been an important feature of this operation. We have found in our own series that only three out of 136, or 2.2 per cent of consecutive cases, showed local recurrence because, we believe, a large area of skin is removed.

It is very important that one should consider the usefulness of the arm, and in the procedure we have done, brought out by W. L. Rodman in 1908, you can get full abduction and extension in all cases. I am not sure that that can be done with any other method as consistently as with this procedure.

A last point is on roentgen-ray treatment. We do not routinely give our patients preliminary roentgen-ray therapy; we do roentgen-ray cases with axillary metastasis, but I am wondering, and would like to ask Doctor Marshall, whether with the use of roentgen-ray he gets an increased number of cases of lymphedema of the arm. We do not know why that happens, but it seems that rontgen-ray may have something to do with it.

DR. WILLARD BARTLETT, St. Louis, Mo.: It was my priceless advantage to have been with Rudolph Virchow in the late nineties, during which time he taught, as you all know, that cancer is a constitutional disease and that the man who once has cancer is bound to die of cancer if something else does not get him along the way. That had just about escaped my recollection until I operated upon a sister of one of my medical friends. She moved to California and I lost track of her. Twenty-six years after the removal of that breast, he wrote me that his sister had died of cancer of the stomach of a cell type different from that found in the breast.

DR. GEORGE G. FINNEY, Baltimore, Md. (closing): I want to thank the discussers of these papers. Dr. Mims Gage just said to me that he is discouraged with the results, and I am frank to say that I agree with him. He has made the suggestion that all women after the age of 40 should have a simple mastectomy as a form of prophylaxis against cancer of the breast. Perhaps this is not such a radical suggestion after all!

DR. HUGH F. HARE, Boston, Mass. (closing): I want to bring out again that our series consisted of 238 consecutive cases of carcinoma of the breast in which large doses of roentgen-ray were administered to each patient. Our series compares favorably with that reported by Doctor Adair, who gave a similar amount of irradiation postoperatively following radical breast dissection. We have given up the idea of doing routine sterilization in the younger age-group because of the psychic effect, but it may be of use in bony metastases in certain instances. If the patient has bone metastases aggravated at the time of the menstrual period and with pain in the opposite breast, then we believe that sterilization by roentgen rays or surgical castration will help. In our experience, it is likely that only between 15 and 25 per cent of the cases will be aided by sterilization. If radiation sterilization is used, an adequate dose should be given to stop all ovarian activity. There is no reason why radiation sterilization should not be as thorough as surgical sterilization.

DR. GUY W. HORSLEY, Richmond, Va. (closing): In reply to Doctor Lehman's question concerning axillary metastasis, of the 39 cases that had surgical castration at the time of the radical operation, 15 had axillary metastasis. Of the ten that are alive and well after five years, four had axillary metastasis at the time of operation, one of these having carcinoma of the breast, bilateral, with metastasis to the axilla.

THE SURGICAL TREATMENT OF SPONTANEOUS CEREBROSPINAL RHINORRHEA*

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CEREBROSPINAL RHINORRHEA is the drainage of cerebrospinal fluid through the nose. It is a well-known clinical entity, usually resulting from trauma but which may result from various other causes or even without known cause. The term "spontaneous cerebrospinal rhinorrhea" is very loosely used in the medical literature. The present report is intended to set-up as a distinct group those cases that are truly spontaneous and to report the surgical cure of three such cases.

DEFINITION

Cases of cerebrospinal rhinorrhea have been variously classified by numerous authors, but perhaps the most complete classification is that of Cairns.[1] This author divides the cases into four groups: (1) those resulting from acute head injuries; (2) those occurring as a delayed complication of head injuries; (3) those resulting from nasal operations; and (4) spontaneous cases. He states that most of the cases in his fourth group are due to intracranial tumors but some may be due to congenital anomalies. It is with a subdivision of Cairns' fourth group that this report is concerned. Truly spontaneous or primary cerebrospinal rhinorrhea is the discharge of cerebrospinal fluid through the nose that occurs: (1) in the absence of trauma (acute head injuries, delayed complications of head injuries such as fistulous tracts, operative trauma); (2) in the absence of infection of the bones of the paranasal sinuses (ethmoid caries, sphenoid necrosis, *etc.*); (3) in the absence of tumors eroding the base of the cranium (osteoma, pituitary tumors, meningiomas, *etc.*); (4) in the absence of prolonged increased intracranial pressure (cerebral tumors, congenital or acquired hydrocephalus); and (5) in the absence of demonstrable congenital anomalies (nasal cephalocele, *etc.*). In short, primary cerebrospinal rhinorrhea is the drainage of cerebrospinal fluid through the nose without definite demonstrable cause.

ETIOLOGY

The definition of primary cerebrospinal rhinorrhea given in the preceding paragraph naturally precludes the establishment of a definite etiology for this condition. However, several possible pathways for egress of the fluid from the cranium into the nose have been suggested. Loftus,[2] and Johnston,[3] have suggested that the fluid escapes through the craniopharyngeal canal as rem-

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nants of this structure can be demonstrated in humans at term. Britt,[4] and Locke,[5] have postulated that the olfactory bulb might maintain its embryonic ventricular lumen and a fistula form from this lumen into the nose, probably along the olfactory nerves. Britt[4] also suggests an opening from the basal subarachnoid cistern through the cribriform plate but does not mention the possible cause of such an opening. Nothnagel,[6] and Cairns,[1] suggest that fluid may escape along the sheaths of the olfactory nerves. Johnston[3] mentions the possibility of holes in the cribriform plate that are deprived of nerve fibers. Adson[7] and Aubin[8] suggest congenital defects of the cribriform plate that permit extension of arachnoid along nerve fibers through the cribriform plate.

The most probable pathway for the escape of fluid in the cases of primary cerebrospinal rhinorrhea is along the olfactory nerves. Each olfactory nerve consists of approximately 20 separate filaments which are axons of olfactory cells in the mucous membrane of the nose. These filaments pass through the cribriform plate of the ethmoid *en route* to the olfactory bulb and are held together in bundles by extensions of the three layers of the meninges. The dura mater joins the periosteum of the nose while the pia mater fuses into the neurolemma of the nerves. The arachnoid usually does not extend through the cribriform plate and when it does the extension is very short.

Locke and Naffziger[9] injected celloidin masses under pressure into the subarachnoid spaces of dogs and noted that there was frequent leakage into the nose. Although this finding could not be duplicated in the human cadaver, it seems probable that in the cases reported here there is an extension of the subarachnoid space along the olfactory nerves into the nose.

It is possible that there is some defective development of the cribriform plate in the cases of primary cerebrospinal rhinorrhea. In the embryo the ethmoidal cartilage consists of a mesial mass which extends from the sphenoid to the tip of the nasal process and of paired masses lateral to the olfactory sacs. The fibers of the olfactory nerve pass between the unjoined mesial and lateral masses. Cartilaginous trabeculae later surround the bundles of nerve fibers and interconnect the three masses. The perforated parts of the completed ethmoid ossify and are then known as the cribriform plates.

The causative agent of the rupture of the arachnoid with consequent escape of fluid, however, is not known. Jauregg[10] has suggested that sneezing might suddenly force open such a pathway. Every theory in the literature for spontaneous rhinorrhea postulates increased intracranial pressure. In the cases reported here there was no evidence of increase in intracranial pressure. The patients did not have respiratory infections or hay fever so that increases in pressure from coughing or sneezing could not play a part. Therefore, although the pathway for the escape of cerebrospinal fluid into the nose is thought to be along the olfactory nerves, the reason for the sudden onset of the rhinorrhea is still unknown.

Although reports of cases of cerebrospinal rhinorrhea abound in the literature, very few of the cases can be properly included in the group here reported. In the reports of Cairns,[1] German,[11] Eagleton,[12] and many

others,[32, 33] there is a definite history of trauma as the etiologic agent of the rhinorrhea. Ten of the eleven cases of Dandy[13] had histories of trauma or occurred postoperatively. Campbell,[14] Learmonth[15] and Donnelly[16] have reported cases following nasal surgery. Som and Kramer,[17] Adson,[7] and others, have reported tumors eroding the floor of the skull with subsequent rhinorrhea. Locke,[5] Meyer,[18] Cushing,[19] and others, have reported rhinorrhea in cases of intracranial neoplasms causing increased intracranial pressure. Aubin[8] reports minor congenital defects at the cribriform plate. None of these cases fall into the category of truly spontaneous or primary cerebrospinal rhinorrhea set-up in the present report. The great majority of cases reported either have a known etiology or the reports are too meager for proper classification. Of the cases reported by St. Clair Thomson[20] only his own case is definitely one of primary rhinorrhea. The remaining cases reviewed had either a definite etiology or insufficient evidence for classification. Johnston[3] reported a case and reviewed the literature on rhinorrhea through 1920. Although some of these cases are almost surely primary cerebrospinal rhinorrhea, the case reports, for the most part, are too inadequate for definite classification. The cases of primary cerebrospinal rhinorrhea found in the literature since 1920 are found in Table I. The propriety of including the case of Adson[7] might well be questioned, as a definite dural defect was found. However, the defect actually was a minor enlargement of the normal opening around an olfactory nerve and as the lesion in the cases here reported is thought to be around the olfactory nerves, it is thought that this case should be included. Two of the cases reviewed showed hyperostosis frontalis interna by roentgenologic examination, but this may have been a coincidental finding. At any rate, the cases are included with reservation.

DIAGNOSIS

Diagnosis of cerebrospinal rhinorrhea is not difficult. Clear fluid drips from the nose almost constantly and if the diagnosis is in doubt, the fluid can be examined by chemical means and shown to be cerebrospinal fluid. Dye can be injected into the lumbar subarachnoid sac and recovered from the nose, as was done by Fox,[21] and in one of the cases in the present report. This test is also of value in determining the side of the leak, a matter of great importance. After it is established that the fluid is cerebrospinal fluid, it is perhaps best to follow the dictum of Locke[2] and consider each case as a "brain tumor suspect." Careful history and examination, including roentgenologic studies, will decide whether or not tumor or any increased intracranial pressure plays a part in the etiology. Trauma or operative procedures can be evaluated by the history. Infections of the sinuses and osteomyelitis of the skull can be diagnosed by examination and roentgen studies. Congenital anomalies, likewise, will usually be discovered by adequate study. If all of the above conditions have been discarded by clinical studies, the case must be considered as one of primary cerebrospinal rhinorrhea.

TREATMENT

There is no unanimity of opinion as to the proper treatment of cerebrospinal rhinorrhea. The early writers, such as Loftus[2] in 1923, felt that any treatment was definitely contraindicated. Feinblatt and Damrau[22] in 1934,

TABLE I

Author	Age and Sex	Duration of Rhinorrhea	Side Affected	Mode of Onset	Treatment	Remarks	Results
Adson[7] 1941	31 Female	9.5 mos.	Not stated		Craniotomy. Opening 2 mm. in diameter around olfactory nerve. All studies negative.	None	Cure immediately
Friedberg & Galloway[24] 1938	38 Female	4 mos.	Right	Followed severe respiratory infection	Intranasal 20% silver nitrate	All studies negative	Flow ceased in 12 days
Plum[27] 1931	45 Female	18 yrs.	Not stated		Three nasal operations	Had severe headaches. Encephalogram revealed cortical atrophy	Flow has diminished but continues
Fox[21] 1933	33 Female	4 mos.	Left	Followed severe respiratory infection	Intranasal 20% silver nitrate	All studies negative	Flow ceased in 4 mos.
Wessels[26] 1939	49 Female	1 yr.	Left	No definite precipitating factor	Craniotomy. Depression in anterior fossa	Evidence of old papilledema; encephalogram was negative	Cure immediately.
Ballon & Ballon[28] 1937	53 Male	1 yr.	Right	Followed severe respiratory infection	None	Positive WaR. All other studies negative	Flow ceased in 5 mos.
Titche[29] 1941	50 Female	Several mos.	Left	No definite precipitating factor	Told to use silver protein in nose	X-rays revealed hyperostosis frontalis interna	Flow continues
Jobson[23] 1941	50 Female	2 mos.	Right	Followed sneezing	Intranasal 10% silver nitrate	All studies negative	Flow ceased in 1 day. Recurred 1 year later. Stopped after similar treatment
Dandy[13] 1944	39 Male	4 mos.	Not noted	No definite precipitating factors	Craniotomy. Both sides explored	All studies negative	Flow continues
Wurster[30] 1937	29 Female	4 yrs.	Right	Followed severe respiratory infection	Argyrol tampons, mild silver protein solution	All studies negative	Flow ceased in 3 years
Feinblatt & Damrau[22] 1934	59 Female	6 wks.	Not stated	No definite precipitating factor	Rest in bed	All studies negative	Flow ceased in 3 weeks
Ameriso[31] 1942	44 Female	15 days	Right	No definite precipitating factor	None	X-rays revealed hyperostosis frontalis interna	Flow continues

felt that any nasal or surgical treatment was contraindicated. However, the extreme danger to life of cerebrospinal rhinorrhea is generally recognized. Certainly, most of the patients with such a leak will eventually develop meningitis, even in spite of modern drug therapy. Rhinologists have tended to treat

cerebrospinal rhinorrhea by intranasal medication and Fox,[21] Jobson,[23] and Friedberg and Galloway[24] have reported cures following the use of silver nitrate, which is painted around the middle turbinate. This method of therapy causes an intense reaction and is open to the objection that intranasal manipulation might well precipitate a meningitis. In addition, intranasal therapy does not attack the rhinorrhea at its most likely source—the cribriform plate. Intracranial operative intervention is the method of choice in the treatment of this condition as modern neurosurgical methods and chemotherapy have largely dispensed with the old objections of danger of meningitis and operative mortality. The exact operative procedure to be followed is still a matter of some debate. Almost all of the surgical methods reported have been directed towards the closing of traumatic fistulae. Cairns[1] employs direct suture of a dural defect or the use of fascia, which has also been advocated by Dandy,[13] Peet[25] and Learmonth[15] have placed iodoform gauze beneath dural defects, while German[11] has turned down small dural flaps from the covering of the crista galli. Graham[34] plugs the opening in the bone with wax. Adson[7] uses a bilateral bone flap and sacrifices both olfactory nerves in order to overlap dura around the fistula and interposes muscle in the suture line. All of the above methods, particularly those using an extradural approach, are open to the objection that the dura over the cribriform plate is very thin and adherent.

The method of surgical treatment advocated here postulates that the leakage of fluid is along the olfactory nerves. In none of the three cases was a dural or bony defect seen but the method of treatment outlined as follows produced immediate cures in all cases with no recurrences. A small frontal osteoplastic flap is reflected on the side of the leak, the skin incision being entirely behind the hair line. The dura is opened around the edges of the bony opening and the frontal lobe retracted (Fig. 1). In no case was there any evidence of pressure and it was not necessary to tap the ventricles, ample space for exploration being secured by emptying the basal cisternae. Careful exploration for tumor or congenital defect is then carried out, such exploration being negative in the cases here reported. The filaments of the olfactory nerve are then pulled out of the cribriform plate and a piece of muscle inserted into the openings in the cribriform plate (Fig. 2). The frontal lobe is then allowed to fall back over this area and the dura is tightly closed with interrupted silk sutures. The bone flap is replaced and the skin closed in usual fashion. In all of the three cases here reported the cessation of leakage of cerebrospinal fluid has been immediate and there have been no recurrences. An essentially similar method of attack was used successfully by Sachs in a case reported by Wessels,[26] and also by Klein[8] in two cases with congenital defects at the cribriform plate. The surgical attack and repair should be entirely intradural.

CASE REPORTS

Case 1.—A female, age 40, white, was admitted to Medical College of Virginia Hospital, March 29, 1943, with complaint of fluid running from her nose. Family and past histories noncontributory. Present illness began two months before admission, when

clear fluid began to drip from the left nostril at the rate of five to six drops every half hour. No history of trauma or upper respiratory infection. No headaches, convulsions or evidence of any cerebral involvement. Physical examination on admission was completely negative except for clear fluid dripping from the left nostril. Blood pressure 124/90. Neurologic examination was completely negative. Roentgenologic studies revealed the sella turcica to be normal in size, with the posterior clinoids somewhat thin. There was clouding of the left antrum and right frontal sinus. No roentgenographic evidence of increased intracranial pressure was present. Lumbar puncture revealed an initial pressure of 110 mm. water, with clear fluid. No cells found. Protein normal. Wassermann reaction negative. Blood and urinalysis entirely normal. Sulfadiazine therapy was

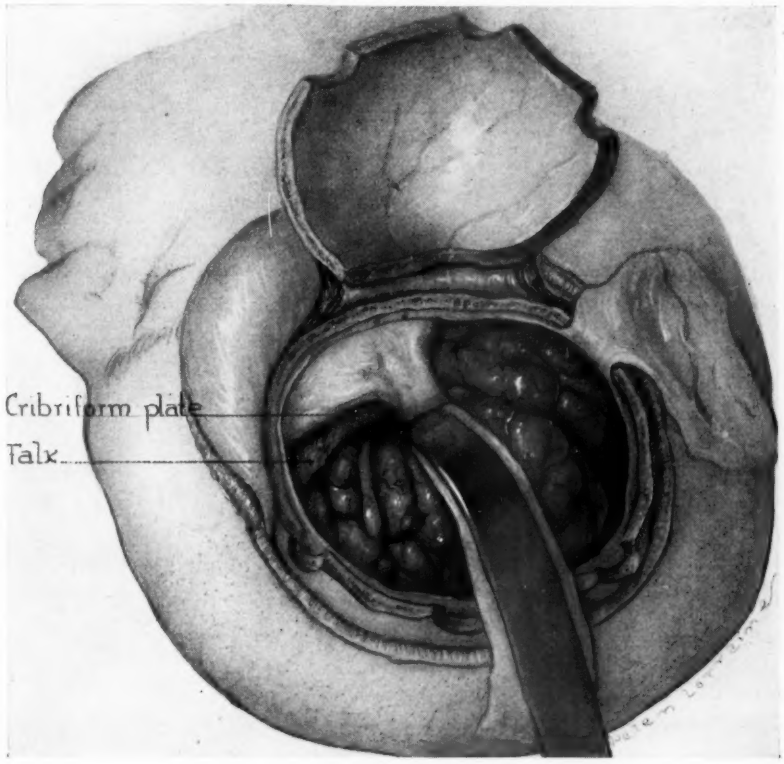

FIG. 1.—Operative exposure of cribriform plate.

instituted. Following lumbar puncture the cerebrospinal fluid ceased to flow. Patient discharged on April 5, 1943. Readmitted April 19, 1943. Eleven days after discharge from the hospital, April 16, fluid again began to drip from left nostril. Patient also complained of severe headache. General and neurologic examinations, again, completely negative. Visual fields full and normal. On April 27 lumbar puncture was done and 1 cc. indigo carmine injected. Fluid from nose was colored blue within 15 minutes. Dry cotton tampons were placed in lateral and superior nasal crevices. Repeated tests showed only the cotton in region of cribriform plate to be discolored. Left frontal craniotomy on April 29, 1943. Technic is outlined in text. No pathology found around sella turcica. The depression of the olfactory bulb seemed a little deep. Cribriform plate sealed-over with

muscle. No drainage of fluid following operation. Patient has continued well in every way (3.5 years postoperative).*

Case 2.—A female, age 50, white, was admitted to Medical College of Virginia Hospital, April 30, 1944, with complaint of watery discharge from left nostril. Family and past histories noncontributory. Present illness began four weeks before admission, with onset of drainage of clear fluid from left nostril. No headache or visual disturbance.

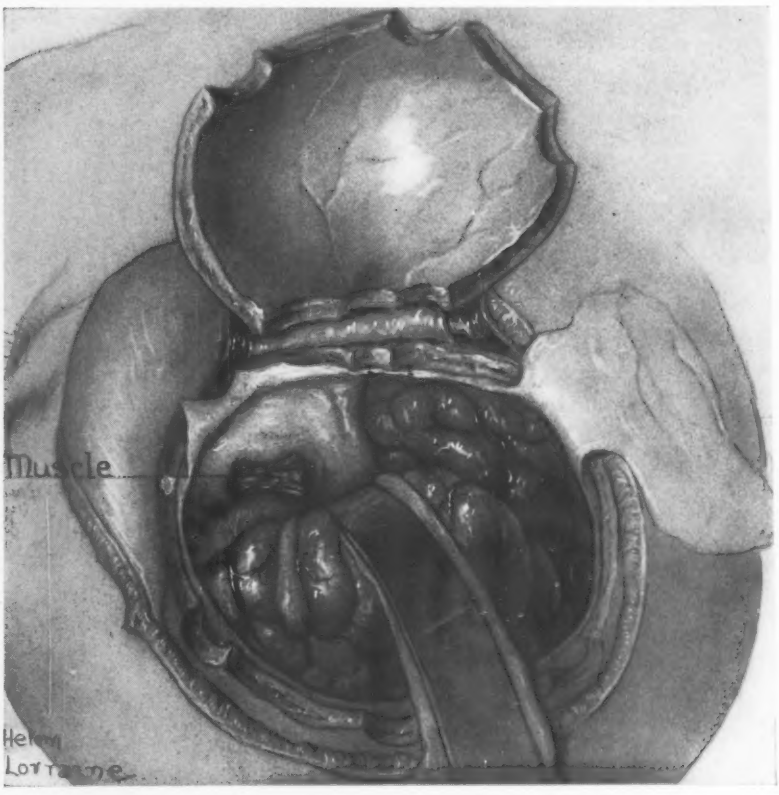

FIG. 2.—Operative exposure illustrating muscle inserted into openings in cribriform plate.

No upper respiratory infection and no history of trauma. Drainage of fluid was constant. General physical examination revealed only drainage of clear fluid from left nostril. Blood pressure 110/80. Neurologic examination was completely negative. Routine blood and urine studies entirely negative. Roentgenologic examination of the skull was entirely negative, the sella turcica being normal in size and not eroded. Ethmoid cells were clear. Rhinologic examination revealed only deflected septum on the left, with deep spur in posterior aspect of middle mentus. Dry cotton localization revealed that fluid was coming from superior nasal space between the middle turbinate and the septum on the left. No anosmia. Operation, May 3, 1944, by technic detailed in text. Operative findings completely negative. Region of left cribriform plate sealed-over with muscle. No further

* See footnote on opposite page.

cerebrospinal rhinorrhea. Discharged May 25, 1944. Patient seen August 22, 1946. Perfectly well (2.25 years postoperative).*

Case 3.—A female, age 50, white, was admitted to Medical College of Virginia Hospital, October 24, 1944, with complaint of drainage of clear fluid from right nostril. Family and past histories were completely negative. Present illness began about two weeks before admission when clear fluid was noted dripping from the right nostril. No upper respiratory infection and no history of trauma. No sneezing. Eleven days after onset of rhinorrhea patient had sudden onset of severe headache and felt that drainage of fluid became more profuse. General physical examination completely negative except for drainage of clear fluid from right nostril. Neurologic examination completely negative. Blood and urine entirely normal by all laboratory studies. Roentgenograms of skull entirely normal. Right craniotomy, October 24, 1944, according to technic detailed in text. No pathology found. Region of cribriform plate sealed-off with muscle. No leakage of fluid following operation. Patient discharged November 10, 1944. October 24, 1946, patient stated that she is perfectly well in every way. (Two years postoperative).

Discussion.—The present report is an attempt to establish as a distinct clinical group those cases of cerebrospinal rhinorrhea that occur without definite demonstrable cause. Although there are innumerable reports of cases of rhinorrhea in the literature, only a few of the cases fall into this category. Undoubtedly, the condition occurs much more frequently than the number of reports indicates, but it seems probable that it is relatively rare. It is desirable to define and segregate these cases as a definite clinical group. The diagnosis, at least for the present, is one of exclusion, as the cases fall into this group only when all demonstrable etiologic agents have been excluded.

A review of the literature reveals 12 cases that fall into the group identified in this report. The great majority of cases have been excluded because of a history of trauma, nasal operations or definite evidence of intracranial tumor. In other instances the cases are too inadequately reported to be sure that they are truly cases of cerebrospinal rhinorrhea or that an intracranial tumor has been eliminated. Five of the cases previously reported had upper respiratory infections either at or immediately before the onset of the rhinorrhea. In none of the cases in this report was there any evidence of such infection. The presence of respiratory infections might well be of some importance because of the suggestion of Werner Jauregg that sneezing might precipitate cerebrospinal rhinorrhea. That such incidents are not the sole precipitating agents is shown, however, by the three cases reported here, in none of which was sneezing a factor.

The etiology of this condition remains in doubt, but it seems most probable that the cerebrospinal fluid escapes along the olfactory nerves. Such a conclusion is given added weight by the cure of the three present cases by intradural occlusion of the points of exit of these nerves with muscle. Very minor congenital anomalies in the region of the cribriform plate can produce openings around the olfactory filaments which allow the arachnoid to extend along the nerves into the nasal cavity. The cause of the rupture of the arachnoid is not

* Cases 1 and 2 were referred by Dr. Roderick MacDonald, of Rock Hill, South Carolina, who reported them in a thesis for the American Laryngological, Rhinological and Otological Society.

as yet determined, however. A marked increase in intracranial pressure could cause the rupture, but in none of the cases in this report was there any evidence of even temporary increased pressure.

Diagnosis of cerebrospinal rhinorrhea is usually not difficult. As mentioned before, it is important to eliminate all possible etiologic agents before the case is considered to be one of primary cerebrospinal rhinorrhea. It is then important to determine the side of the leak, and this can usually be done by inspection of the nasal cavity. Increased certainty is added by the injection of dye into the lumbar canal and viewing its exit into the nose.

Primary cerebrospinal rhinorrhea is an entity that requires prompt treatment. Although some cases have been reported of long duration, they are certainly exceptions to the usual course. The logical point of attack is at the cribriform plate, as this is the almost certain seat of the underlying pathology. The various methods of surgical approach have been reviewed in the text and the authors' method detailed. By this method the presumed seat of pathology is directly attacked and only one olfactory nerve is sacrificed. The efficacy of this method of attack is attested by the results obtained in three cases.

SUMMARY

1. A group of cases exhibiting cerebrospinal rhinorrhea without demonstrable cause is defined as primary cerebrospinal rhinorrhea and set-up as a clinical entity.

2. The literature is reviewed and 12 cases tabulated as probably belonging to this group.

3. Possible sites for escape of cerebrospinal fluid into the nose are discussed and the probable site suggested.

4. A surgical treatment for this condition is detailed, and three cured cases reported.

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DISCUSSION.—DR. FRANC D. INGRAHAM, Boston, Mass.: It is a great pleasure to hear this interesting paper by Doctor Coleman and Doctor Troland on rhinorrhea which seems to be spontaneous. Since it is a relatively uncommon condition I might add a word about three similar patients seen on our service. All three were female patients and in two instances the onset was associated with sneezing during the course of a respiratory infection. One patient had severe hypertension and exploration was considered unwise. The leak stopped spontaneously and somewhat later she succumbed to cardiovascular disease. At autopsy, a very careful examination of the cribriform plate was made but no abnormal opening was demonstrated. In the second case a congenital defect, perhaps 5 mm. in diameter, was exposed at operation although it could not be seen in the roentgenograms. In the third case a fracture was demonstrated although there had been no history of trauma elicited. It would seem likely that injury might be a causative factor in some of these cases although nothing in the history would point to it. As far as treatment is concerned, Doctor Coleman and Doctor Troland have shown that this technic is effective and has the great advantage of preserving the olfactory endings on one side.

DR. BARNES WOODHALL, Durham, N. C.: I am sorry Doctor Coleman could not be here and I trust that he will soon recover from his distressing accident. I am delighted to discuss this paper, since Doctor Troland is an old friend and colleague of mine.

However, I know little about this rare neurosurgical problem. After reading the title of this paper on the program, I reviewed our material and could find only two cases that could be defined as possibly primary cerebrospinal rhinorrhea. On further study, the first case was proven to be a stenosis of the aqueduct of Sylvius and the rhinorrhea ceased following a Trokildsen's procedure performed by Dr. Guy Odom. The second case was that of a woman, age 50, who sneezed vigorously and immediately developed a profuse rhinorrhea. At that time I investigated the pertinent literature and found that, among the few things that could be done, was the application of silver nitrate in the nose. However, she was placed in a sitting position following several spinal punctures and the rhinorrhea ceased and she has not returned to our hospital. I am very glad to know about Doctor Troland's findings in this perplexing syndrome and I shall be guided by them in the future if I should encounter another case.

DR. ERNEST SACHS, St. Louis, Mo.: We have had two cases which may truly be classed as spontaneous cerebrospinal rhinorrhea. One was operated upon by Doctor Furlow and one by myself. I think, in the first place, he is absolutely right. This condition must be attacked intracranially and attacked promptly. In the second place, until we get further information, it would seem the best thing to do, which is what we did in our cases, is to remove the olfactory fibers on the side on which the leak occurs and plug the bone with some substance, such as muscle. We think muscle is better than fibrin foam or fascia. We found no evidence of congenital defect and no etiologic factor in our cases; both patients were women. Just why that should be I do not know. Certainly, it is all important to tackle the thing from the intracranial approach and do it promptly and not let them continue to leak, even though an occasional one might heal spontaneously.

DR. CHARLES E. TROLAND, Richmond, Va. (closing): I want to express my appreciation to Doctors Ingraham, Woodhall and Sachs for their discussion. In one of the cases we reported the patient stopped leaking fluid following lumbar puncture but soon came into the hospital again leaking fluid. Personally, I believe it is increased intracranial pressure that causes rupture of the arachnoid, but in no case could we definitely determine what caused the increased pressure. We agree with Doctor Sachs that muscle rather than fascia is the proper tissue to be used, and definitely feel that fibrin foam and gelatin foam are not as desirable materials as muscle.

TETRA-ETHYL-AMMONIUM AS AN ADJUNCT IN THE TREATMENT OF PERIPHERAL VASCULAR DISEASE AND OTHER PAINFUL STATES*

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THE DEMONSTRATION by Acheson and Moe[1, 2] that in animals the tetra-ethyl-ammonium ion† will block transmission of nerve impulses through autonomic ganglia led to extensive investigations of the effects of this drug in man. Preliminary observations of its usefulness as a diagnostic and therapeutic agent in various disease states have been previously reported by Lyons,[3, 4] Berry, and coworkers.[5]

It is the purpose of this report to present in detail the clinical observations derived from a large series of patients suffering from peripheral vascular disease and allied disorders who received one or more injections of tetra-ethyl-ammonium for the purpose of producing an autonomic blockade, and to attempt to clarify from the results obtained the exact rôle played by the autonomic nervous system in these particular disease states and the benefits to be derived from single or multiple autonomic blockades.

PHARMACOLOGY OF TETRA-ETHYL-AMMONIUM

Sufficiency data[1-4] has been made available to make unwarranted any detailed description of the pharmacology of the tetra-ethyl-ammonium ion in this paper. Suffice to say that the ganglionic blocking action of tetra-ethyl-ammonium has been shown to be its most prominent effect when administered parenterally to animals. A brief consideration of the clinical and pharmacologic observations supporting this contention may be listed as follows:

1. Following the parenteral injection of tetra-ethyl-ammonium there is a fall in both systolic and diastolic blood pressure. This is not the result of the direct action of the drug upon the arterioles since intra-arterial injection produces no change, whereas intravenous injection produces an increase in peripheral blood flow. This increase in peripheral blood flow may be demon-

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† Furnished as tetra-ethyl-ammonium chloride ("Etamon") by Parke, Davis and Company, Detroit, Michigan, in 20-cc. sterile ampules, through the courtesy of Dr. E. C. Vonderheide.

strated clinically either by plethysmographic recordings or controlled thermocouple studies.

2. The drug produces no further fall in blood pressure after destruction of the medulla or transection of the cervical cord in the experimental animal (vasomotor tone absent). If the transected cervical cord, however, is stimulated, thus, restoring vasomotor tone, the injection of tetra-ethyl-ammonium will then produce a fall in blood pressure.

3. The injection of tetra-ethyl-ammonium does not prevent the direct peripheral action of epinephrine even where the latter is infused to produce a restoration of blood pressure after destruction of the vasomotor center of the medulla. Despite the restoration of blood pressure by the administration of epinephrine, the depressor response to tetra-ethyl-ammonium is still held in abeyance.

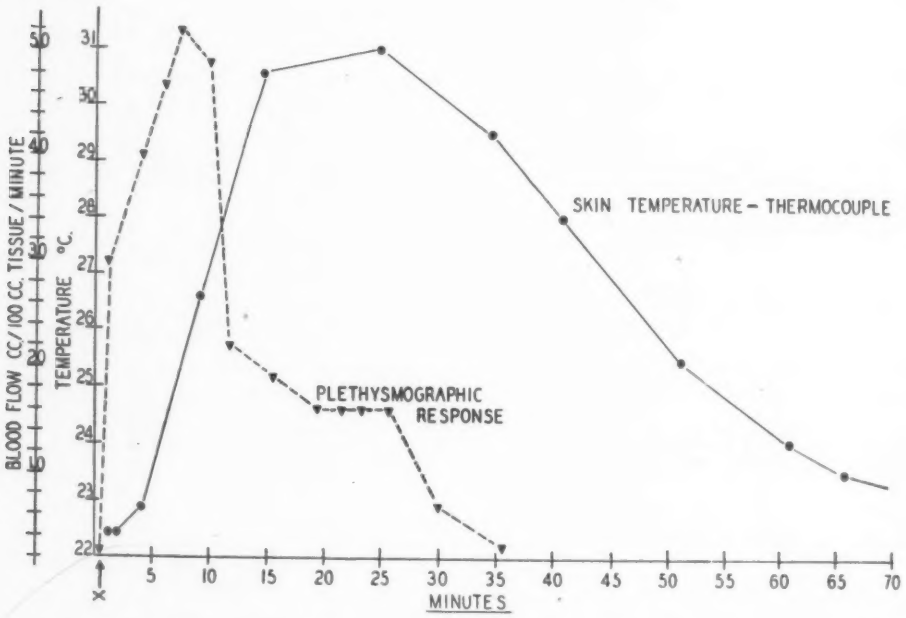


FIG. 1.—Peripheral blood flow response (foot) in a patient with functional vascular disease as measured by plethysmography and skin temperature (thermocouple) recordings following the intravenous administration of 500 mg. tetra-ethyl-ammonium. Note the delay in thermal response and the marked increase in blood flow from 0.24cc./per minute/per 100 grams of tissue to 5.2 cc./per minute/per 100 grams of tissue.

4. In animals, following the administration of the drug, preganglionic stimulation (stellate) produces no change in heart rate. Postganglionic stimulation under identical conditions produces a slowing of heart rate, evidence that the site of action of the drug lies within the ganglion.

5. Following parenteral administration of tetra-ethyl-ammonium, preganglionic stimulation of the cervical sympathetics to the nictitating membrane in animals is ineffective in producing a contraction of this membrane. Under identical conditions, however, postganglionic stimulation is effective, further evidence that the site of action of the drug lies within the ganglion.

6. Peripheral blood flow to the extremities as measured by plethysmography or thermocouple temperature recordings is increased following the injection of the drug in man (Fig. 1).

7. In man, in addition, there is dilatation of the pupil, loss of accommodation, cessation of sweating, dry mouth, and postural hypotension for varying periods of time following the injection of the drug.

8. Tetra-ethyl-ammonium produces cessation of gastro-intestinal motility as observed fluoroscopically and by roentgenograms,[20] and atony of the bladder as measured by cystometric studies.[6]

9. The pain of angina pectoris and coronary thrombosis is obliterated following injection of tetra-ethyl-ammonium in spite of a possible decrease in coronary blood flow and a definite further fall in blood pressure. Other types of visceral pain are likewise ameliorated.[4]

10. Clinically, no action of the drug can be demonstrated in a sympathectomized extremity, whereas evidence of sympathetic block can be demonstrated in a normal control extremity in the same individual.[5]

CLARIFICATION OF TERMINOLOGY

The term "vasospasm" is used herein to refer to an *abnormal* degree of vasoconstriction of blood vessels which is manifested by the clinically-evident signs and symptoms of coldness, hyperhidrosis, mild cyanosis and pain.

The term "functional component" is used herein with reference to the presence or absence of vasodilation or vasoconstriction, which are expressions of normal physiologic function. If a blood vessel is capable of vasodilatation a functional component is said to be present. In the presence of marked organic changes in the blood-vessel wall, *i.e.*, arteriosclerosis or thromboangiitis obliterans, the vessel may be incapable of undergoing dilatation, hence, the functional component is said to be absent.

The term "autonomic blockade" is used with reference to the temporary paralysis of the ganglia of the autonomic nervous system following the injection of tetra-ethyl-ammonium.

METHOD OF STUDY EMPLOYED

Details of the clinical use of tetra-ethyl-ammonium for diagnostic and therapeutic autonomic blockade have been reported elsewhere.[4, 5] In brief, the patient is placed in a recumbent position, extremities uncovered, in a room of suitable and preferably constant temperature (68°–75°F.). Thermocouple temperature recordings for control were taken from symmetrical points of the extremities under study. Measurements from the peripheral portion of the digits have been usually taken for graphic recording (Fig. 2). Following suitable control studies, tetra-ethyl-ammonium (chloride or bromide) was injected intravenously or intramuscularly in a 10 per cent solution. The intravenous dose employed ranged from 100 mg. (1 cc.) to a maximum of 500 mg. (5 cc.). Considerable care was taken as regards the rate of injection, a minimum of 15 to 60 seconds being ordinarily employed and constant observation of the pulse volume and general reaction of the patient being utilized as a guide to cease or delay further administration of the drug. *Under no circumstance was more than 500 mg. (5cc.) employed as the intravenous dose.* It should be pointed out that this amount of the drug is not always necessary to produce an autonomic blockade, in elderly patients with advanced arteriosclerosis or

in labile patients with functional vascular disease, both of whom are sensitive to autonomic blockade. Previous experience with the reaction of the patient to the injection of the drug was found to be the safest guide in subsequent administrations. It was noted that many patients experienced little difficulty from the injection of tetra-ethyl-ammonium if they had had previous experience with autonomic blockade carried out in this fashion, tolerating maximal doses (5cc.) without untoward systemic effects.

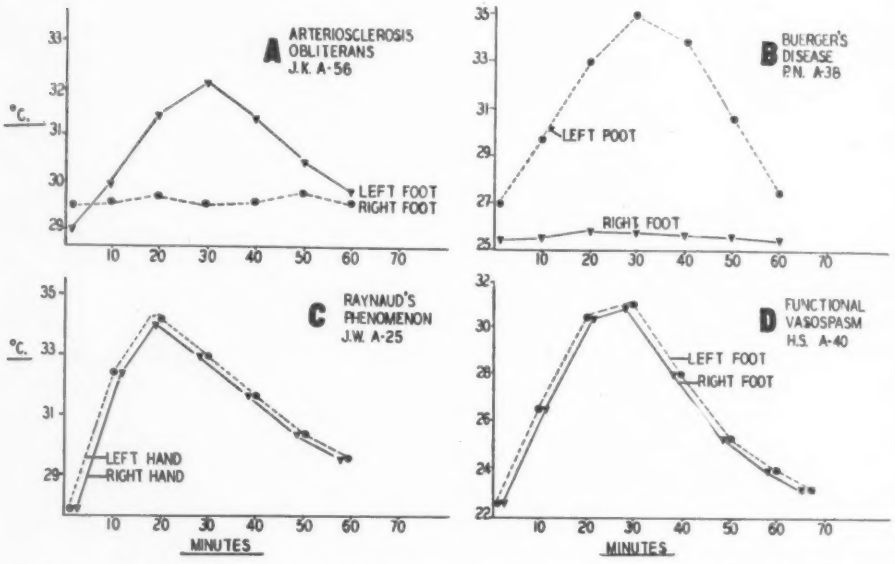


FIG. 2.—Peripheral skin temperature responses in patients with organic and functional vascular disease measured at a room temperature between 68°–70°F. before and after ganglionic block with tetra-ethyl-ammonium.

A. Arteriosclerosis obliterans. The response in the right foot demonstrates marked occlusive changes with an absence of vasodilatation. The left foot has a normal response.

B. Buerger's disease. The right foot is the site of advanced occlusive changes. A marked functional response is present in the left foot.

C. Raynaud's phenomena. The right and left hands demonstrate an equal temperature response. No evidence of organic occlusion.

D. Functional vasospasm. Starting with an initially low temperature, the right and left foot respond equally without evidence of organic occlusion.

At times it has been noted that the initial injection of tetra-ethyl-ammonium does not produce satisfactory effects in patients in whom it would be reasonable to assume that such a blockade should be effected. Often, however, a satisfactory response can be obtained by repeating the injection on subsequent days. The explanation of this phenomenon is not clear. The rapid excretion of tetra-ethyl-ammonium makes untenable the postulation that this is a cumulative effect of the drug. The presence of fear on the part of the patient with an increased out-put of adrenalin might conceivably nullify the action of tetra-ethyl-ammonium.

THE DIAGNOSIS OF CAUSALGIA AND SYNONYMS APPLIED TO RELATED STATES

Little if anything has been added to the original description of causalgia written by Mitchell in 1864. The frequent finding of osteoporosis in the affected extremity (Sudek's atrophy) and the definite rôle of the sympathetic nervous system as regards the propagation of pain (Leriche) have been little added to over the ensuing year. However, as a result of various authors describing different stages of the same process, a variety of synonyms has accumulated, each of which, in a sense, represents a type of what is more widely recognized as being causalgia, but, in essence, not necessarily having the exact features originally described by Mitchell. To cite a few,[7, 8, 10, 11] acute atrophy of bone, stupeur arterielle, reflex arterial spasm, trophic edema of bone, minor causalgia, traumatic vasospastic dystrophy, reflex sympathetic dystrophy, chronic traumatic edema, peripheral trophoneurosis, posttraumatic osteoprosis, and Sudek's atrophy have all been used to designate either the original state, as described by Mitchell, or a manifestation of the same process. It is recognized, for example, that early in the course of events, vasodilatation may be present and bone atrophy absent. Later, vasoconstriction (vasospasm) and osteoporosis are more frequently encountered.

From the history or examination of the patient, the following sequence of events will usually establish a diagnosis of causalgia or reflex sympathetic dystrophy.[7, 8, 15] These findings and history represented the basis for diagnosis in this series:

1. A history of previous trauma, sometimes almost insignificant and usually, but not necessarily, involving periarticular, vascular or nerve tissues (venous thrombosis, lacerations, gunshot wounds, old fractures, sprains, dislocations, phlebitis or periphlebitis, hematomas, crushing injuries, burn scars, puncture wounds, amputations, *etc.*).

2. Abnormal or disproportionate prolongation of pain, usually directed peripherally to hand or foot, following no known anatomic distribution of nerves, and typically of a burning or aching character which may progress in severity and is characteristically aggravated by manipulation, temperature change, auditory, visual and emotional stimuli.

3. The occurrence of vasomotor phenomena over a time-interval disproportionate to the initial trauma with a tendency toward diffusion and extension. Early vasodilatation, temperature change, color change, hyperhidrosis, edema. Later, evidence of vasoconstriction (vasospasm), chronic periarticular edema and fibrosis, atrophy, hyperhidrosis, osteoporosis and waxy pallor, with almost pathognomonic hygromania in the severe cases.

4. A frequent affectation of the morale of the sufferer (Leriche).[11] (Anxiety states, psychoneuroses, suicidal tendencies, drug addiction, inferiority patterns).

5. The frequent roentgenographic demonstration of early cystic or late diffuse osteoporosis in the involved extremity, (Sudek's atrophy) usually in association with immobilization, atrophy, periarticular fibrosis and ankylosis of joints. This must be differentiated from osteoporosis due to other causes.

6. Cessation of pain and/or amelioration of the clinical picture following blocking or extirpation of the sympathetic ganglia supplying the involved

areas. (Leriche,[11] de Takats,[7] Mahorner,[9] Allbritten,[12] Evans,[8] White,[19] *etc.*). Certain advanced cases may have no relief (subjectively) of their difficulties despite sympathectomy, rhizotomy or even cordotomy. Under such circumstances, the pain is said to be "thalamic" and will respond, if at all, only to sensory decortication.[7]

Table I summarizes the results of treatment with tetra-ethyl-ammonium of six patients classified as having a true causalgia.

Patients with causalgia and related states may not present themselves for examination with all of the diagnostic features listed. Pain may actually be absent or minimal despite all of the other signs of causalgia being present. Such a situation has given rise to the term "reflex sympathetic dystrophy."[8] The occurrence of edema may be the outstanding feature—hence, the synonym chronic posttraumatic edema. In general, however, if the time elapsed has been sufficient, other collateral evidence is usually available and no difficulty is encountered in correctly classifying the patient's malady. Table II summarizes the results of treatment of 14 patients with tetra-ethyl-ammonium classified under the category of posttraumatic painful states.

The following case reports are presented to illustrate the utilization of tetra-ethyl-ammonium as a diagnostic, prognostic and therapeutic measure in patients with causalgia and posttraumatic painful states.

CASE REPORTS

B. S., Col. male, age 53. Patient was admitted to the Neurosurgical Service, 8-29-'46, complaining of severe pain in the left hand and forearm. He gave a history of receiving a shotgun injury to the left upper arm, 1-11-'46, which was operated upon elsewhere. The details of this procedure were not known. The patient experienced pain immediately following the operation which had gradually increased in intensity to the point where he was unable to move the left upper extremity for fear of aggravating the pain. He experienced some relief by constantly keeping the hand covered in a moist towel (hygromania). The pain was of a burning, aching character and unlocalized.

Examination revealed a colored male carefully guarding his left upper extremity, the hand of which was wrapped in a wet towel. He had the typical facies of a patient in constant pain. Detailed examination of the hand and arm was impossible. There was a healed scar on the posteromedial aspect of the left upper arm. The skin was smooth and shiny and obvious atrophy of musculature was present. There was incomplete ankylosis of the elbow, wrist and joints of the hand. The skin of the hand was hyperesthetic to stimulation, and the elbow and hand were maintained in a flexed position. A marked temperature gradient was present, as was evidence of excessive sweating (seen later). Later examination revealed complete ulnar and incomplete median nerve palsy. Roentgenologic examination revealed marked patchy osteoporosis involving the distal ends of the radius and ulna, the bones of the wrist and hand being extensively involved with the exception of the proximal portion of metacarpals 2–5, inclusive. This was interpreted as being a Sudek's type osteoporosis.

The patient received tetra-ethyl-ammonium, I. V., 250–500 mg. on four occasions for the purpose of producing a sympathetic block. Following each of these administrations, pain ceased for a varying interval of time and the patient was able to carry out joint movements with greater ease. Accordingly, 9-7-'46, an upper dorsal sympathectomy was performed. Immediate relief of pain was experienced by the patient. Exploration of the median and ulnar nerves in the scar site was contemplated for the near future.

TABLE I

SUMMARY OF THE RESPONSE TO TREATMENT WITH TETRA-ETHYL-AMMONIUM IN PATIENTS WITH CAUSALGIA

Case	Name	Age	Sex	Etiologic or Initiating Factors	Duration Pain or Symptoms	Number Autonomic Blocks*	Total Dose, Milligrams	Duration Treatment	Result of Treatment and Duration of Benefit	Final Diagnosis
3	B.D.	19	F	Gunshot wound of thigh, peroneal palsy (partial).	12 mos.	11	5,500	Periodic + 1 week daily I.V.	Immediate cessation pain, which lasted few hours. Gradual increase in duration relief. Discharged ambulatory and free of pain.	Causalgia (lower extremity) following gunshot wound of thigh with partial peroneal nerve palsy.
5	E.D.	48	F	Crush injury of finger.	25 mos.	17	8,500	3 weeks Daily I.V.	Definite relief of pain and amelioration of edema, with improvement in joint motion and use of extremity (temporary).	Causalgia (upper extremity) following crush injury of finger. Psychoneurosis. Sympathectomy indicated but not advised. (See case history.)
7	L.L.	34	F	Minor burn of finger, subsequent cellulitis hand. Abscess forearm, chronic drainage.	7 mos.	6	3,000	1 week Daily I.V.	Patient admitted temporary alleviation pain following each injection but required frequent administration opiates.	Causalgia following chronic tenosynovitis forearm. ?Median palsy. Morphine addiction. (See case history.)
8	M.L.	59	F	Old fracture. Dislocation head of radius.	2 mos.	6	8,700	1 week Daily I.V. and I.M.	Definite temporary improvement (5 hours/injection) in symptoms. Later gradual disappearance original pain.	Causalgia (upper extremity) following old fracture—dislocation, with partial median nerve palsy. Resection radial head advised.
18	B.S.	53	M	Gunshot wound left arm. Radial-ulnar palsy.	8 mos.	4	1,600	1 week I.V.	Temporary cessation pain (3–5 hours/injection). Sympathectomy, with relief pain.	Causalgia (upper extremity) following gunshot wound, with ulnar-radial palsy. Neurolysis contemplated.
19	M.S.	55	F	Radial N. palsy following trauma left upper ext. P.O.	1 mo.	5	2,450	Daily I.V.	Pain relief and greater mobility—sustained. Definite psychogenic element present.	Postoperative (hysterectomy), injury left brachial plexus, with causalgia and radial nerve palsy. Still under treatment.

* With tetra-ethyl-ammonium.

TABLE II

SUMMARY OF THE RESPONSE TO TREATMENT WITH TETRA-ETHYL-AMMONIUM IN PATIENTS WITH POSTTRAUMATIC PAINFUL STATES

Case	Name	Age	Sex	Etiologic or Initiating Factors	Duration Symptoms	Number Autonomic Blocks*	Total Dose Milligrams	Duration Treatment	Result of Treatment and Duration of Benefit	Remarks	Follow-up
1	E.W.	46	F	Multiple Trendelenburg procedures. ?Injury brachial plexus.	6 mos.	15	7,100	5 weeks Periodic I.V.	Complete sustained relief of pain. 90% improvement in mobility. Minor temperature. Recurrence 4 months.	?Injury brachial plexus. Reflex sympathetic dystrophy. Causalgic pain, periarthritis.	6 mos.
2	D.L.	54	F	Old fracture of humerus. Unsupported "hanging cast."	5 mos.	15	7,200	8 weeks Periodic I.V.	Original pain ceased in 24 hours. Approximate 75% improvement in mobility.	Old fracture—posttraumatic edema, intractable pain, periarthritis.	5 mos.
4	M.M.	29	F	Operations both feet age 12. Long immobility in encasements.	17 yrs.	11	5,500	Periodic + 1 week daily I.V.	Prompt cessation pain. Gradual sustained subsidence edema. ?Improvement in mobility.	Chronic Posttraumatic edema, with periodic vasospasm. Chronic posttibial tenosynovitis.	5 mos.
6	R.B.	25	M	Old shrapnel wounds popliteal fossa. Previous symptoms and neurectomy.	18 days	5	2,500	Periodic 1 week I.V.	Sustained relief pain after 3rd block. Previous sympathectomy and neurectomy.	Old shrapnel wounds popliteal fossa. ?Primary vasc. disease. Recurrent intractable pain.	4 mos.
9	O.K.	50	M	Open reduction ununited fracture. Posttraumatic edema, with vasospasm and cyanosis.	3 days	3	1,300	Daily (3) I.V.	Rapid subsidence edema and vasospasm. Other conservative measures had failed. Cessation pain.	Posttraumatic edema, with vasospasm following open reduction for ununited fracture.	3 mos.
10	P.B.	35	F	Old trauma to ankle. ?Phlebitis, with vasospasm.	11 mos.	4	2,000	Periodic I.V.	Immediate cessation pain (1–5 hours)—unsustained. Slight improvement edema. Sympathectomy with relief.	Old trauma to ankle. Intractable pain and swelling. Vasospasm.	6 mos.
11	H.H.	48	F	P.O. open reduction forearm. Vasospasm and edema.	3 days	3	600	Daily I.V.	Rapid subsidence edema and vasospasm which had not responded to other measures.	Posttraumatic edema with vasospasm following open reduction forearm.	7 mos.
12	L.M.	54	F	Old trimalleolar fracture, with prolonged immobilization.	5 yrs.	5	2,400	3 weeks Periodic I.V.	Minimal improvement in edema and pain. No response.	Old tri-malleolar fracture. Traumatic arthritis. Intractable pain and swelling.	5 mos.
13	S.T.	53	F	Old fracture of elbow. Multiple manipulations.	5 wks.	3	1,500	3 days I.V.	Complete subsidence pain. Gradual subsidence edema. Slight improvement joint mobility.	?Underlying Paget's disease, with pathologic fracture. ?Myositis ossificans.	6 mos
14	E.E.	65	M	Farm accident, with injury to shoulder.	4 mos.	7	3,500	Daily 1 week I.V.	Complete pain relief. Subsidence edema 24 hours.	Brachial plexus injury. Fracture of spine of scapula. Sudek's atrophy of bone.	3 mos.
15	R.C.	62	M	Old trauma to foot. Prolonged immobilization.	9 mos.	1	500	1 day I.V.	Definite improvement in pain and edema Incomplete follow-up.	Posttraumatic painful state. Further therapy advised.	.....
16	A.S.	48	M	Old Colles's fracture. Immobilization.	4 mos.	1	500	1 day	Definite improvement in pain and edema. Incomplete follow-up.	Posttraumatic painful state. Further therapy advised.	.....
17	M.Z.	67	M	Old injury spine. P. O. herniated nuc. and neurectomy.	7 yrs.	4	2,000	1 week I.V.	Immediate unsustained improvement (28 hours) with each block.	Posttraumatic painful state. Further therapy advised.	6 mos.
20	V.W.	60	F	Trauma left arm.	yrs.	1	250	1 day I.V.	No response. Failure. Psychoneurosis.	Previous sympathectomy. Minor causalgia, with Sudek's atrophy of bone.	.....

* Tetra-ethyl-ammonium.

M. L., white, female, age 59. Admitted to the Orthopedic Surgery Service (Dr. Carl Badgley), 2-16-'46, giving a history of having sustained a fracture-dislocation of the right elbow on 12-27-'45. Treatment had been carried out elsewhere and consisted of manipulation under anesthesia and plaster encasement. The day following this procedure, she had noted numbness in the thumb, index, and middle fingers in the right hand. At the end of two weeks in plaster encasement she had experienced considerable pain, edema of the hand, and difficulty moving the fingers. At the time of admission, 2-16-'46, the patient complained of burning pain radiating from the olecranon peripherally into the hand. Examination revealed hyperesthesia to touch, definite increase in sweating and trophic changes in the involved extremity. There was marked limitation of elbow motion, and the patient guarded the extremity carefully; a typical partial median nerve palsy was present. The patient had also required frequent doses of morphine to allay the pain. Relief of distress had also accompanied the use of wet bandages on the involved hand.

Injections of tetra-ethyl-ammonium, I. V. and I. M. were given daily, with definite relief of pain averaging five hours duration, total fractional dose 8,700 mg. Consideration was then given to resection of the head of the radius or dorsal sympathectomy being carried out. Because of the questionable presence of an early myositis ossificans, the patient was discharged home to return for further consideration in one month. She returned, 4-12-'46, at which time improvement was steady and pain was absent or slight. No operative intervention was deemed advisable. She returned again, 4-26-'46, showing considerable return of function in the involved arm and recurrence of pain in the elbow only. The original causalgic type pain had disappeared. Myositis ossificans was present in the area of fracture. Resection of the head of the radius was advised.

B. D., white, female, age 19. First seen in consultation, 2-4-'46, at which time the patient gave a history of having received a gunshot wound of the thigh one year previously (2-5-'45). The through-and-through wound was treated at a local hospital and healed uneventfully. The patient, however, complained of pain in the foot of an aching character, loss of control of the foot several days after operation, and experienced marked tenderness to pressure (attempted walking) and hypersensitivity to cold. An incomplete peroneal nerve palsy was present. Later, she developed moderate edema of the foot and limitation of ankle motion and was unable to bear weight on the extremity. The pain became persistent and increased slowly in intensity.

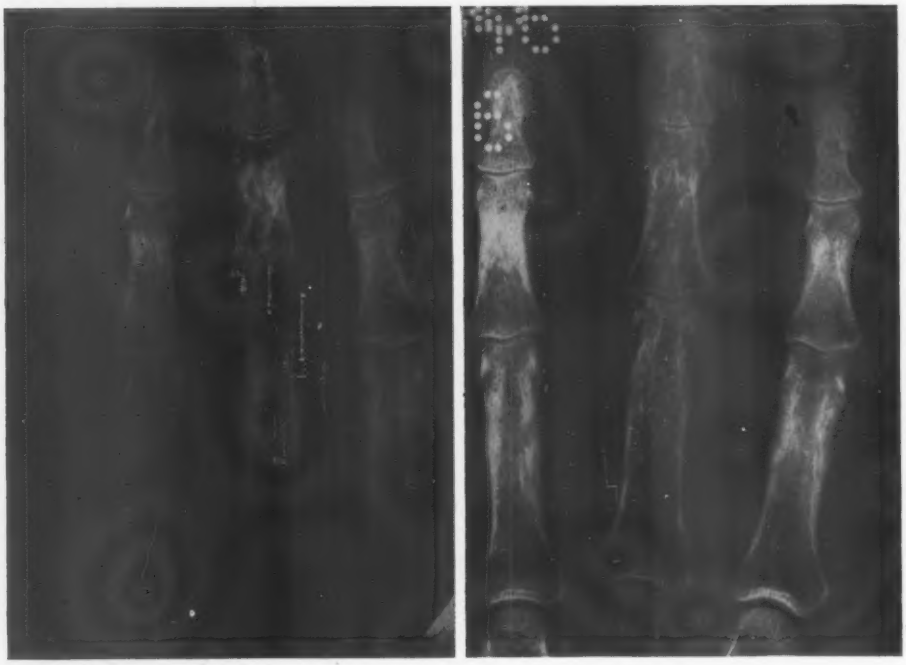
Examination on first admission revealed an incomplete peroneal palsy, atrophy of the lower leg, a moist cold foot which was tender on palpation, with some hyperesthesia of the skin around the ankle and dorsum of the foot. The patient could walk only with crutches and held the involved leg in a semiflexed position. A cyanotic reticular-livedo was present in involved extremity.

Tetra-ethyl-ammonium, 500 mg. I. V., produced a 4.5°C. rise in temperature of the toes bilaterally. The reticular-livedo immediately disappeared, and within a few minutes, all pain in the extremity ceased.

Because of the time interval which had elapsed since the initial trauma, lumbar sympathectomy was advised.

The patient was not seen again for several months (8-3-'46) at which time the tetra-ethyl-ammonium injection was again repeated, with similar results, and sympathectomy again advised. She returned to the clinic, 8-21-'45, at which time a program of daily sympathetic blocks utilizing tetra-ethyl-ammonium I. V. was instituted. Thereafter, nine such blocks were carried out, total fractional dose of 4,100 mg. being administered. The patient experienced immediate cessation of pain after each injection, pain relief gradually increasing to a point where it failed to return. The patient was ambulatory at this time. She was discharged pain-free and advised to return at intervals for follow-up examinations. Two weeks after discharge, a note from the patient reported that the pain recurred for brief intervals only, and that in general her condition was satisfactory.

E. D., white, female, age 48. The patient was first seen in the Department of Neurosurgery (Doctor Peet) on 8-5-'46. She gave a history of being well until 6-16-'44, at which time she sustained a minor injury to the second finger on the left hand when it was caught between a casting and guard on a rubber wheel. She was treated locally and continued working. Three days later the patient became aware of a stinging sensation in the distal phalanx which finally involved the entire finger. She was seen by the plant physician who splinted the finger and also started contrast baths, massage, manipulations, heat and roentgenotherapy. The pain continued to become more severe and changed to a burning-aching sensation, with diffusion and extension to hand, arm and shoulder. (The pain reached the shoulder approximately one year following the initial trauma.) Subsequently, the patient was examined by several physicians, all of whom concurred in a



A B

FIG. 3.—A. Localized Sudek's osteoporosis associated with causalgia (December, 1944).

B. Roentgenographic findings in August, 1946. The osteoporosis is still largely confined to the phalanges of the middle finger.

diagnosis of psychoneurosis. Only one examining physician pointed out the numerous signs of causalgia present in the patient (severe burning pain, glossy skin, temperature changes, excessive sweating, hyperesthesia, and osteoporosis). This physician instituted local blocks and mecholyl ointment therapy. At the time of admission to the University Hospital the patient held the arm in a protected position, any contact being painful.

Examination revealed an obese female, demonstrating loss of joint motion particularly involving the wrist and fingers, shiny, glossy, atrophic skin on the hand, decreased temperature in the involved hand, hysterical clonus of the second finger and marked hyperesthesia. Roentgenologic examination and comparison with previous films brought by the patient (Fig. 3) demonstrated posttraumatic osteoporosis mainly confined to the 3rd left digit.

The patient was given daily injections of tetra-ethyl-ammonium—total fractional dose 8,500 mg.—17 injections. Definite relief of pain and obvious improvement in function gradually became demonstrable although the patient herself was loath to acknowledge (but did acknowledge) the benefits obtained. Although it was felt that sympathectomy would undoubtedly have relieved the patient, no surgical intervention was advised because of the irrevocable psychogenic element present. Periodic conservative therapy was therefore advised. Final diagnosis: causalgia-like pain with superimposed psychoneurosis. Localized Sudek's atrophy, pariarthritis and fibrositis.

E. E., white, male, age 65. First seen in consultation, 8-13-'46, giving a history of having been run-over by a farm machine, 4-23-'46, at which time he sustained a bruised

FIG. 4.—Marked osteoporosis of bones of the right hand and wrist following injury to shoulder four months previously.

right leg and right shoulder and a small laceration of the ear. Upon attempting to again run the machine, the patient fainted and the accident again recurred. He was placed at bed rest by his physician, the only complaint of the patient being periodic paresthetic shocks "like electricity" shooting down his right arm. Subsequently, the shoulder girdle and arm developed burning pain which increased in intensity. Because of this pain, joint motion was considerably impaired.

Examination revealed a tendency to winged-scapula, with questionable atrophy of the right infraspinatus muscle. The hand was thin and atrophic in appearance and hyperesthetic to touch. There was practically no scapulo-thoracic motion and the fingers were held in a partially flexed position. There was a ⅞-inch atrophy of the arm and a ⅝-inch atrophy of the forearm. Periarthritic edema and fibrosis was present in the hand.

Roentgenograms revealed generalized osteoporosis of the right shoulder girdle, hand and wrist, an old ununited fracture of the spinous process of the right scapula and an old healed fracture of the 5th metacarpal (Fig. 4).

The patient was treated with tetra-ethyl-ammonium to obtain a sympathetic block on seven occasions, (total fractional dose 3,500 mg.). He experienced immediate relief of pain, which gradually abated and eased following the course of therapy. The periarthritic edema and joint motion improved considerably and the patient was finally transferred back to the Orthopedic Service for manipulation of the various joints of the upper extremity under anesthesia, to attempt to lessen the ankylosis due to periarthritic fibrosis.

A summary of our experiences in treating patients with causalgia, and related posttraumatic painful states, is presented in Table IV. The history and clinical findings of these patients are listed in Table III. It will be noted that ten out of 20 cases had sustained relief of symptoms following repeated autonomic blockades with tetra-ethyl-ammonium. (Follow-up 2–6 months.) In general, however, such benefits in many instances were also related to periodic physiotherapy, which was carried out during the pain-free periods following autonomic blockades and which could only be carried out with difficulty at any other time. In the opinion of the authors, autonomic blockades which produce symptomatic relief in this group of patients does not remove the indications for appropriate sympathectomy. The use of tetra-ethyl-ammonium, however, at repeated intervals, has produced satisfactory results in certain patients in whom sympathectomy would have been desirable but was not felt to be feasible because of the presence of a marked psychogenic element or unstable personality.

Herpes Zoster and Postherpetic Neuralgia: Following the report by Findley and Patzer[16] of the benefits derived from paravertebral procaine block in the treatment of herpes zoster, it was deemed advisable to attempt treatment of these patients by autonomic blockade with tetra-ethyl-ammonium (See Table V). Nine patients in this series were treated, therefore, with repeated injections of tetra-ethyl-ammonium usually at daily intervals. There were five males and four females, with an average age of 59 years (range 31–76). Five of these patients had postherpetic neuralgia, usually of long duration. The remaining four patients had acute or subacute herpes zoster. Each patient received an average of eight autonomic blocks with tetra-ethyl-ammonium (range 2–14) over an average period of 11 days. Three patients received intravenous and intramuscular therapy combined.

As a result of this therapy, 100 per cent of the patients obtained some relief of pain varying from a very brief period to six hours per block. The more sustained improvement occurred in the patients with acute or subacute herpes zoster and the least benefit was derived by those patients with old postherpetic neuralgia. This is in agreement with therapy carried out by paravertebral procaine blocks.

In general, younger patients responded better than older patients, although this was not invariably true. It was also noted that patients with herpes involving the cranial nerves were afforded the shortest interval of pain relief.

TABLE III

SUMMARY OF THE HISTORY AND CLINICAL FINDINGS IN 20 PATIENTS WITH CAUSALGIA AND VARIOUS POSTTRAUMATIC PAINFUL STATES

Case	Name	Age	Sex	Initiating Factors	Pain	Sensation Skin	Color Changes	Edema	Periarthritis and Fibrositis	Sweating	Atrophy	Osteoporosis	Diagnosis
1	E.W.	46	F	Injury brachial plexus.	Aching, burning	Hyperes.	Waxy pallor	Moderate	Marked	Minimal	Minimal	Minimal	Reflex sympathetic dystrophy.
2	D.L.	54	F	Old fracture humerus.	Aching, burning	Hyperes.	Waxy pallor	Marked	Marked	Minimal	Minimal	Marked	Reflex sympathetic dystrophy.
3	B.D.	19	F	Gunshot wound thigh.	Aching, burning	Hyperes.	Blotchy livedo	Minimal	Moderate	Cold Moderate	Moderate	.....	Causalgia.
4	M.M.	29	F	Bone surgery and encasements	Feet aching	Hyperes.	Pallor flush	Marked	Minimal	Moderate	Minimal	Minimal	Posttraumatic edema.
5	E.D.	48	F	Crush injury finger.	Fingers aching	Hyperes.	Waxy pallor	Moderate	Marked	Minimal	Moderate	Marked	Causalgia.
6	R.B.	25	M	Shrapnel wounds.	Feet aching	Hyperes.	Flush (infection)	Minimal	Moderate	.....	Marked	Marked	Reflex sympathetic dystrophy.
7	L.L.	34	F	Chronic infection hand and forearm.	Hand-arm aching	Hyperes.	Pallor cyanosis	Minimal	Marked	Moderate	Moderate	Marked	Causalgia. Drug addiction.
8	M.L.	59	F	Old fracture-dislocation.	Aching, burning	Hyperes.	Pallor cyanosis	Moderate	Marked	Marked	Moderate	Moderate	Causalgia.
9	O.K.	50	M	Open reduction nonunion fracture	Mild	.....	Pallor	Marked	.....	Minimal	.....	Marked	Posttraumatic edema.
10	P.B.	35	F	Old trauma to ankle.	Aching foot	Local hyperes.	Livedo	Marked	Minimal	Moderate	Minimal	.....	Reflex sympathetic dystrophy.
11	H.H.	48	F	Open reduction radius.	Aching fingers	Local hyperes.	Marked cyanosis	Marked	Limited	Moderate	.....	.....	Posttraumatic edema.
12	J.M.	54	F	Old trimalléolar fracture.	Painful foot	.....	Bluish cyanosis	Marked	Minimal	Moderate	Moderate	Moderate	Traumatic arthritis. ?Reflex dystrophy.
13	S.T.	53	F	Old fracture elbow.	Aching arm	Hyperes.	Glossy pallor	Marked	Moderate	Minimal	.....	Marked	Reflex dystrophy. ?Paget's dis.
14	E.E.	65	M	Injury to shoulder.	Aching, shooting arm	Hyperes.	Waxy pallor	Moderate	Marked	Minimal	Marked	Marked	Posttraumatic state.
15	R.C.	62	M	Old trauma to foot.	Burning ankle	Hyperes.	Pallor, cyanosis	Moderate	.....	Minimal	Moderate	Marked	Posttraumatic edema.
16	A.S.	48	M	Old Colles's fracture	Burning hand	Hyperes.	Waxy, erythema	Marked	Marked	Marked	Moderate	Marked	Posttraumatic state.
17	M.Z.	67	M	Spine injury. P. O. Disc.	Burning heels	.....	Normal	Moderate	Minimal	Minimal	Marked (old)	Moderate	Posttraumatic state.
18	B.S.	53	M	Gunshot wound arm.	Tingling, aching	Hyperes.	Glossy	Moderate	Marked	Marked	Marked	Marked	Causalgia.
19	M.S.	55	F	Brachial plexus injury.	Burning, aching	Hyperes.	Waxy pallor	Moderate	Marked	Minimal	.....	Minimal	Causalgia.
20	V.W.	60	F	Trauma to arm.	Burning, aching	Hyperes.	Waxy pallor	Minimal	Marked	.....	Moderate	Marked	Posttraumatic state. Previous sympathectomy.

Even so, many of these patients requested further therapy with tetra-ethyl-ammonium. In general, the response of the patient to the relief afforded by autonomic blockade with tetra-ethyl-ammonium was one of satisfaction or encouragement although it was recognized that in several of the older patients no permanent relief was being obtained.

The exact rôle played by vasospasm in patients with herpes zoster was difficult to interpret and further experience with this form of therapy will be necessary before any clear-cut decisions can be reached as regards the mechanism of pain relief by autonomic blockade. A summary of our experience in utilizing tetra-ethyl-ammonium in patients with herpes zoster and postherpetic neuralgia is presented in Table V.

TABLE IV

CAUSALGIA AND POSTTRAUMATIC PAINFUL STATES
STATISTICAL ANALYSIS OF TABLES I AND II

Cases	20
Etiology or initiating factor.	
Soft tissue trauma	11
Fractures	7
Unknown (P. O.)	2
Associated complete or partial nerve palsy	5
Duration of symptoms	
Less than 1 month	3
More than 5 years	4
Average of 7 months	13
Sex-incidence.	
Females	13
Males	7
Average age	48
Average number of ganglionic blocks	7
Average total dose of tetra-ethyl-ammonium (mg.)	3,330
Symptomatic relief—20 cases.	
Temporary	6
Sustained	10
Sympathectomy	4
No follow-up	2
Failures (tetra-ethyl-ammonium)	2

FUNCTIONAL VASCULAR DISEASE

It was pointed out in a previous report[5] on the effects of tetra-ethyl-ammonium on functional vascular disease that there was usually a marked response as regards blood pressure and rise in peripheral skin temperature (Fig. 2). The variation in duration of the response to autonomic ganglia blockade by tetra-ethyl-ammonium was pointed out. Further experience with this form of therapy in this group of patients has not modified the previously reported useful purposes of this form of ganglionic block in these patients: (1) the injection of tetra-ethyl-ammonium obviated the necessity of single or multiple paravertebral blocks; (2) it was helpful in demonstrating the presence of a functional vascular component especially in patients with scleroderma; and (3) it aided the establishment of a diagnosis. With further

TABLE V

SUMMARY OF THE TREATMENT OF PATIENTS WITH HERPES ZOSTER AND POSTHERPETIC NEURALGIA BY REPEATED AUTONOMIC BLOCKADE WITH TETRA-ETHYL-AMMONIUM

Number	Name	Age	Sex	Duration	Location	Blocks	Total Dose (Mg.)	Period Treated	Response to Treatment	Diagnosis
1.	E.A.	73	F	Months	D_5-D_7 and left arm postherpetic neuralgia	6	2,150	6 days	Pain relief 1–4 hours per block, with nocturnal recurrence†	Postherpetic neuralgia
2.	A.S.	58	F	Weeks	Thoracic girdle pain. Residual lesions present	14	6,600	16 days	Ninety % improvement in two weeks—sustained.	Subacute herpes zoster
3.	U.O.	76	M	Years	Postherpetic neutralgia D_{11}-D_{12}-L_1	13	6,500	17 days	Improvement after second block. 50–75% sustained pain relief.	Postherpetic neuralgia
4.	J.F.	61	M	Years	Face, scalp and neck, right.	7	3,500	7 days	Temporary minimal relief of pain without definite improvement.	Postherpetic neuralgia
5.	S.P.	45	F	Days	Left occiput and postcervical area, severe, acute	11	5,500	16 days	Immediate relief of pain. Marked improvement after third block—sustained	Acute herpes zoster
6.	A.M.	57	M	Years	First division of trigeminal nerve	6*	4,100	12 days	Immediate relief of pain (6 hrs. per block). Unsustained. Temporary improvement only.	Postherpetic neuralgia
7.	C.W.	55	M	Weeks	First and second divisions trigeminal nerve	7*	4,800	14 days	Temporary improvement. Pain intensity decreased and controlled with salicylates.	Subacute herpes zoster
8.	W.W.	76	M	Years	D_8 dermatome	9*	5,500	10 days	Temporary relief with each block. Chordotomy produced questionable relief.	Postherpetic neuralgia
9.	D.S.	31	F	Days	Herpes labialis of the perineum	2	750	2 days	Imm. relief pain 5–6 hrs. per block. Rapid subsidence	Acute herpes zoster

* Intravenous and intramuscular therapy combined.
† Paravertebral procaine block yielded identical results.

experience, the impression has been gained that tetra-ethyl-ammonium offers much to be desired as a therapeutic measure in these patients even when used at repeated intervals. Its diagnostic value is self-evident. Many of the patients with functional vascular disease have a marked sensitivity to their environment, *i.e.*, cold and psychic stimuli, and whereas the injection of tetra-ethyl-ammonium may produce a remarkable clinical alleviation of the vascular symptoms and picture, the factor of *time* intervenes, and with the disappearance of the ganglionic block, susceptibility to a recurrence of the attacks occurs. The injection of the drug has proven of value in fulminating functional vascular disease in our experience, and it is also our impression that in certain of the patients with Raynaud's phenomena, attacks have been aborted or modified in their intensity. With the exception of these circumstances, the utilization of tetra-ethyl-ammonium as a therapeutic measure has proven of little benefit. Our original impressions of its value as a diagnostic procedure have been greatly strengthened with added experience. It has in no sense replaced

TABLE VI

FUNCTIONAL VASCULAR DISEASE

CLASSIFICATION OF PATIENTS WITH FUNCTIONAL VASCULAR DISEASE IN WHOM TETRA-ETHYL-AMMONIUM WAS USED AS A DIAGNOSTIC OR THERAPEUTIC MEASURE

Raynaud's phenomena (primary and secondary)	16	Associated scleroderma	6
Livedo-reticularis	4	Disseminated lupus	1
Acrocyanosis	2		
Unclassified (environmental response)	7		
Pernio	1		
Total	30		

the value of sympathectomy in this group of patients. Table VI lists the classification of patients with functional vascular disease in whom tetra-ethyl-ammonium was used as a diagnostic or therapeutic measure.

ORGANIC OCCLUSIVE ARTERIAL DISEASE—BUERGER'S DISEASE

The opportunity of studying the effects of tetra-ethyl-ammonium in some 35 patients with thrombo-angiitis obliterans has been afforded within the past year. The average age of these patients was 40 years, and the average duration of symptoms five years, indicating an onset of the disease in most instances at age 35. There was only one female in the entire series. Fifty per cent of the patients were habitual smokers when first seen in the clinic. In the 35 cases, 71 extremities were involved and 40 per cent of the patients had an associated active or inactive superficial thrombophlebitis. Eight patients presented themselves initially either with a history of previous amputation (toe, foot, leg) or underwent some form of amputation subsequent to admission because of established gangrene or progressive suppurative infection. Diagnostic autonomic blockade alone was carried out in 16 of the 35 patients, largely for the

demonstration of any functional component that might exist. This particular group included those patients referred for diagnosis alone, patients with far-advanced occlusive arterial disease, or in whom infection or gangrene of a significant degree was already established and required more definitive therapy than autonomic blockade. In the remaining 19 patients, autonomic blockade with tetra-ethyl-ammonium was utilized both as a diagnostic and therapeutic measure, the latter largely to relieve vasospasm, if present, afford pain relief, improve claudication or aid in the amelioration of active superficial migratory thrombophlebitis. Tetra-ethyl-ammonium was utilized as a diagnostic measure in the sense of affording a prognosis of benefits to be derived were sympathectomy carried out. A total of ten lumbar sympathectomies was performed in this series of patients. Nine of these were carried out on the basis of the response to autonomic blockade with tetra-ethyl-ammonium. Therapy with repeated autonomic blockades, utilizing tetra-ethyl-ammonium was carried out in eight of the 19 patients for pain alone, in seven patients for claudication

TABLE VII

THROMBO-ANGIITIS OBLITERANS
THE RESULTS OF THERAPY WITH TETRA-ETHYL-AMMONIUM IN PATIENTS WITH THROMBO-ANGIITIS OBLITERANS

	Cases	Early to Mod. Advanced	Far-advanced or Terminal
Relief of pain (temporary or sustained)	12	8	4
Improvement in claudication	11	11	0
Active phlebitis	4	3	1

	Functional Component Present (Vasodilation-Vasoconstriction)		Absent
Relief of pain	12	10	2
Improvement in claudication	11	10	1

unassociated with severe rest or nocturnal pain, and in four patients with symptoms of pain and claudication combined. Four of these patients also presented themselves with active superficial migratory phlebitis. In the series of patients with Buerger's disease treated with repeated intravenous injections of tetra-ethyl-ammonium—each patient received an average of six autonomic blocks, (range 2–18), usually given at daily intervals, but in some instances at longer intervals largely dependent upon the response of the patient to this therapy in conjunction with other conservative measures, and the availability of the patient for treatment. The results of treatment in this manner as regards relief of pain and claudication are illustrated in Table VII.

In the nine patients in this series who underwent lumbar sympathectomy on the basis of their previous response to tetra-ethyl-ammonium, 100 per cent achieved results classified as good to excellent, *i.e.*, if pain had ceased following a test dose of tetra-ethyl-ammonium, or if a functional component had been

previously demonstrated by the thermocouple measurements and visible clinical improvement, similar results were achieved with sympathectomy as predicted by the response of the patient to tetra-ethyl-ammonium. In those patients available for postoperative study, the skin temperature response to sympathectomy under like conditions of room temperature was found to be amazingly identical to the reeordings made preoperatively following injection of tetra-ethyl-ammonium.

Table VII illustrates graphically the relationship of the presence or absence of a functional component and the severity of the disease process to the results obtained in patients with thrombo-angiitis obliterans treated by autonomic blockade. It will be noted that patients with an early to moderately advanced process experienced significant improvement either in severity of their pain or amelioration of their claudication. None of the far-advanced or terminal cases had improvement in claudication with this therapy. If a functional component was established, some benefit was derived from autonomic blockade in most instances. It is of interest to note, in addition, that some of the cases first treated successfully in this manner have sustained their improvement over a 12-month period, without reactivation of their disease process. This is not entirely due, of course, to therapy with autonomic blockade alone.

Certain definite impressions have been derived from treating this series of patients with thrombo-angiitis obliterans by repeated autonomic blockades with tetra-ethyl-ammonium. They are as follows:

1. The response to the injection of the drug (either plethysmographic response or skin-temperature recordings with a thermocouple) can be utilized as an excellent gauge of the degree of occlusion and collateral circulation in the arterial vessels of the extremities (Figs. 1 and 2).
2. The response to the injection of the drug has been found reliable when used to predict the response in the involved extremities to appropriate sympathectomy.
3. Tetra-ethyl-ammonium has afforded relief of pain in numerous instances, particularly rest pain, and in some cases irrespective of the presence of a functional component or vasospasm. The cessation of pain, following injection of the drug, has at times been extremely rapid. Pain relief has at times been temporary and at times sustained, particularly if therapy is repeated at appropriate intervals. The duration of relief of pain has borne no fixed relationship to duration of autonomic block.
4. The injection of tetra-ethyl-ammonium is followed by visible, palpable and measurable relief of vasospasm when such is present clinically.
5. The injection of the drug has been of no avail in the presence of severe infection or established gangrene in this series of patients.

The following case reports are presented to illustrate in Case H. M. the improvement in claudication and pain following a three-week period of daily autonomic blockades, and Case E. B. to illustrate a bizarre, yet highly satisfactory control of intractable pain in a patient with far-advanced thrombo-angiitis obliterans and drug addiction.

CASE REPORTS

H. M., age 29, Jewish male, first seen in the Surgery Clinic on 10-8-'46. The patient was in excellent health until December, 1945, at which time he began to experience pain in his calves of a spontaneous nature and not aggravated by exercise. Two weeks later he noted the onset of pain in his hands and subsequently observed the development of numbness, coldness and cyanosis of the toes and fingers. He was seen at another clinic in August, 1946, at which time a "thrombosed vein" was excised from the superficial area of his calf. He gave a history of smoking one-half to one package of cigarettes daily, and the occurrence of night pains in his calves and feet. There had been a recent development of intermittent claudication (2 blocks).

On physical examination, findings of note were limited to the lower extremities. In the right foot, the posterior tibial pulse was absent and there was an aberrant dorsalis pedis pulse present along the lateral malleolus. In the left foot, the dorsalis pedis pulse was absent, the posterior tibial pulse was palpable. Elevation of both legs produced a cyanotic mottling and marked pallor of the right great toe. The venous filling time of the right foot was sluggish as compared to the left foot. Dependency produced a cyanotic rubor of the right great toe. Thermocouple studies revealed a temperature gradient of 7.2°C. on the right leg and 7.8°C. on the left leg.

The patient was given 500 mg. of tetra-ethyl-ammonium chloride intravenously. Thirty minutes later, no rise in temperature had occurred in the right lower extremity and a 4°C. rise in temperature had occurred in the left foot.

From the history, physical findings, and response to autonomic blockade a diagnosis of thrombo-angiitis obliterans was made. A functional component on the left leg and organic occlusion in the right leg was demonstrated.

Thereafter the patient received a series of 16 daily intravenous injections of tetra-ethyl-ammonium chloride to produce a sympathetic block. *These were administered by his own physician.* He returned, 11-8-'46, one month after having first been seen in the clinic. At that time, practically all claudication had ceased, the patient was experiencing no night pains and he expressed the opinion that his condition was 95 per cent improved. He was advised to return at intervals for reëxamination.

E. B., age 43. The patient had been seen at the University Hospital at intervals over a period of several years. In 1943 he had developed typical intermittent claudication and rest-pain in his extremities. These symptoms had gradually increased in severity to the point of invalidism from constant pains. A diagnosis of thrombo-angiitis obliterans was made in December, 1943, the most active process being in the left lower extremity.

Left lumbar sympathectomy was carried out subsequently in June, 1944. During this operative procedure the left ureter had been injured and a left nephrectomy was ultimately necessitated in August, 1944. Convalescence was satisfactory and all pain in the left lower extremity had ceased.

The patient inadvertently injured the right great toe in November, 1944, and a supracondylar amputation was carried out elsewhere for established gangrene.

The patient returned to the Surgery Clinic, 8-19-'46, in a state of chronic invalidism and drug addiction (dilaudid). He was suffering from a bizarre distribution of severe pain of a constant nature involving the stump of the amputated limb, the site of the nephrectomy scar, and the site of the sympathectomy scar. There was also a recurrence of the burning pain in the left lower extremity (previously sympathectomized). The patient had been receiving dilaudid gr. 1/16 q. 3 h., day and night, for the previous three months in an effort to relieve his painful state.

The essential findings in the physical examination were extremely sensitive, tender scars in the left flank, pain on light pressure over the scar in the amputation stump, and absence of all pulses in the left lower extremity, with the exception of the femoral pulse. The clinical impressions were: (1) Thrombo-angiitis obliterans, with severe ischemic

neuritis; (2) drug addiction (dilaudid); (3) phantom limb pain; (4) postoperative neuralgia (scars); and (5) psychoneurosis.

Inasmuch, as the history and physical findings pointed to a far-advanced occlusive arterial disease and because sympathectomy had been carried out previously, and drug addiction was now present, it was not considered that much aid could be given the patient from a series of autonomic blockades. The patient was hospitalized, however, and a series of eight injections of tetra-ethyl-ammonium I. V. carried out. A total dose of 4,000 mg. was administered in a one-week period. During this interval all narcotic medication was stopped and the patient successfully endured the expected withdrawal symptoms. Marked alleviation of pain was noted following the fourth sympathetic block. The bizarre pains were gradually lessened in intensity and finally disappeared. The personality change in the patient was remarkable. He stated that he now felt better than he had for several years. The patient became ambulatory on crutches, and was discharged home without medication.

The conversion of a "basket-type" case of terminal Buerger's disease, with drug addiction, into a pain-free ambulatory patient, in whom analgesics were unnecessary, as a result of repeated autonomic blockades was difficult to reconcile. The case is reported, however, to emphasize the possibility that the autonomic nervous system may be important from other standpoints than vasospasm alone, in patients with vascular disease. It was also considered that, inasmuch, as the patient tolerated the withdrawal of large amounts of dilaudid, that pain had actually been present and had ceased with the therapy given.

PERIPHERAL ARTERIOSCLEROSIS OBLITERANS

To date, approximately 125 patients with peripheral arteriosclerosis obliterans have received tetra-ethyl-ammonium as a diagnostic, prognostic or therapeutic measure. In a previous report[5] it was pointed out that the drug had proven useful in two respects in these patients: (1) aiding in the control of nocturnal pain; and (2) as an index of the possible benefits that might be derived from a lumbar sympathectomy. The experience gained since the original report has done nothing to modify the impressions previously obtained other than to fortify them. The occasional arteriosclerotic evidences a rather surprising improvement in claudication following autonomic blockade with tetra-ethyl-ammonium, but it should be emphasized that this is not the usual experience with this group of patients. The injection of the drug, will, of course, not modify established gangrene. The occasional patient with arteriosclerosis obliterans demonstrates a surprising degree of functional response (vasodilatation) following the injection of tetra-ethyl-ammonium. For this reason, all patients with symptomatic peripheral arteriosclerosis are tested accordingly, since, in our experience, such patients demonstrate marked benefits from lumbar sympathectomy. On the other hand, lack of response to the drug is not a contraindication for operation (sympathectomy) primarily, because the factor of *time* is not taken into consideration. Given sufficient time, following lumbar sympathectomy, many arteriosclerotics evidence satisfactory improvement despite an absence originally of any demonstrable functional component or response to sympathetic block, autonomic block, or spinal anesthesia (Fig. 2). This impression has been gained from observations on 40 lumbar

sympathectomies in patients with peripheral arteriosclerosis obliterans—many of whom have now been followed over a considerable time-interval.

Certain dangers inherent to the administration of tetra-ethyl-ammonium in this group of patients are discussed under the section in this paper describing toxic effects.

THROMBOPHLEBITIS

Tetra-ethyl-ammonium has presented an excellent clinical tool for evaluation of therapeutic benefits to be obtained from autonomic ganglion blockade in thrombophlebitis.[17, 18] Twenty-six cases of thrombophlebitis, in all stages of its progression, have received tetra-ethyl-ammonium either as a therapeutic procedure or in an attempt to evaluate the degree of vasospasm present. Five patients received only one injection as part of their diagnostic work-up. The remaining 21 patients have received two or more injections as a definitive therapeutic measure. Twenty-one cases have been classified as chronic, four as subacute, and one as acute, based upon the duration of their symptoms and physical findings. Edema of some degree was present in all patients treated, as was pain or leg discomfort. Vasospasm was identified in 52 per cent of the treated cases, as manifested by hyperhidrosis, pain, mild cyanosis, coldness and demonstrable vasoconstriction.

Excellent response to repeated autonomic ganglion blockade was observed in the one acute case and in three treated cases of subacute thrombophlebitis. Marked pain relief occurred in a matter of hours and in a few days there was little, if any, residual edema.

Individuals suffering from the resultant effects of chronic thrombophlebitis noted subsidence of edema, relief from congestive pain and a new sense of well-being, as regards the involved extremity. Relief of vasospasm was welcomed by those who, for many years, had been distressed by a cold, moist limb. The duration of the response to ganglionic block was variable, at times extending over a period of days, or longer. Occasionally the benefits derived were of brief duration.

It is of interest to note that in a separate study of chronic thrombophlebitis in 100 patients whose cases were chosen at random from the code room of the hospital, 81 returned at an average interval of 2–3 years following the onset of their disease complaining of pain. Ninety-one of 96 recorded findings in the 100 cases demonstrated edema, and pain and edema were present together in 76 of 96 records of symptomatology. The benefits derived from periodic autonomic blockade with tetra-ethyl-ammonium, while in no sense curative, afforded sufficient temporary relief from pain and edema in these patients to provide a highly satisfactory interval-form of therapy. The patients with deep chronic thrombophlebitis were, for the most part, highly pleased with this form of treatment despite its recognized limitations.

Table VIII is self-explanatory in the listing of symptoms present, duration of the disease and response to antonomic blockade in 21 patients with thrombophlebitis in all the stages of its progression. The five remaining patients received diagnostic blockade only, with a single injection.

TABLE VIII

THROMBOPHLEBITIS

SUMMARY OF THE CLINICAL HISTORY, SIGNS AND SYMPTOMS AND RESPONSE TO TREATMENT OF PATIENTS WITH THROMBOPHLEBITIS

Number	Name	Age	Sex	Duration of Symptoms	Extremity Involved	Edema	Pain	Dermatitis	Pigmentation	Ulceration	Vasospasm	Total Treatment	Total Dosage (Mg.)	Impressions
1.	W.L.	45	M	6 wks.	R. leg	Marked	Mod.	.....	.....	.....	.....	14	7,000	Marked diminuition of pain in 48 hours; complete subsidence of edema in 4 days
2.	M.M.	53	F	9 mos.	Both legs	Mod.	Marked	.....	.....	.....	.....	13	6,500	Symptomatic relief of pain for long periods of time; edema controlled with elastic support.
3.	L.B.	44	F	26 yrs.	L. leg	Marked	Min.	.....	Mod.	.....	.....	11	5,500	Satisfactory improvement of both pain and edema; symptomatic relief of tiredness and heaviness.
4.	E.M.	36	F	20 yrs.	Both legs	Marked	Mod.	Min.	Mod.	.....	Marked	9	4,500	Excellent relief of subjective symptoms; edema subsided and controlled with elastic support.
5.	L.T.	55	F	30 yrs.	L. leg	Marked	Mod.	Mod.	Marked	Mod.	.....	9	4,500	Moderate improvement in edema and pain; no improvement in ulceration during limited period of treatment.
6.	C.R.	49	M	6 wks.	L. arm	Min.	Mod.	.....	.....	.....	.....	9	4,500	Complete subsidence inflammatory process left arm; no recurrence to date.
7.	R.G.	22	M	4 yrs.	Both legs	Marked	Mod.	Mod.	Marked	Marked	Mod.	11	5,500	Complete resolution of edema and controlled with elastic support; all ulcerated areas healed well.
8.	T.E.	31	M	4 mos.	L. leg	Marked	Marked	.....	.....	.....	.....	8	4,000	Complete subsidence of edema in 7 days controlled with elastic support; rapid improvement pain and temperature.
9.	M.W.	31	F	5 yrs.	L. leg	Mod.	Mod.	.....	Min.	.....	Marked	8	4,000	Leg less painful; edema subsiding slowly; moderate relief of ease of fatigue of leg.
10.	H.M.	45	F	20 yrs.	Both legs	Mod.	Mod.	.....	Mod.	.....	Marked	6	3,000	Legs no longer ache; rest pain gone; edema is improved.
11.	M.S.	30	F	5 yrs.	L. leg	Mod.	Mod.	.....	.....	.....	Marked	4	2,000	Periods of edema less often and severe; excellent relief of vasospasm; subjective improvement.

TABLE VIII—*Continued*

THROMBOPHLEBITIS

SUMMARY OF THE CLINICAL HISTORY, SIGNS AND SYMPTOMS AND RESPONSE TO TREATMENT OF PATIENTS WITH THROMBOPHLEBITIS

Number	Name	Age	Sex	Duration of Symptoms	Extremity Involved	Edema	Pain	Dermatitis	Pigmentation	Ulceration	Vasospasm	Total Treatment	Total Dose (Mg.)	Impressions
12.	R.S.	20	F	24 hrs.	L. arm	Marked	Marked	.....	.....	.....	.....	4	2,000	Marked subsidence of pain and edema in 24 hours; venous pressure remained high, however, at time of discharge from hospital.
13.	P.B.	35	F	11 mos.	R. leg	Min.	Marked	.....	.....	.....	Marked	4	2,000	Old calf vein thrombosis secondary to injury; immediate relief of pain after injection; subsequent lumbar sympathectomy produced complete alleviation of symptoms.
14.	K.D.	28	F	5 yrs.	L. leg	Mod.	Min.	.....	.....	.....	Marked	3	1,500	Edema subsiding; leg less tired and congestive pain has improved; vasospasm not as severe.
15.	B.C.	56	M	6 mos.	L. leg	Marked	Mod.	.....	.....	.....	Marked	5	2,500	Marked reduction in swelling and congestive pain; severe coronary infarct necessitated cessation of treatment. Subsequent death from coronary thrombosis.
16.	F.D.	52	F	20 yrs.	L. leg	Marked	Mod.	Mod.	Mod.	Marked	Marked	3	1,500	Subjective improvement; edema less marked; observation period to date too short to observe improvement in ulcerations.
17.	E.H.	46	F	2 yrs.	Both legs	Mod.	Mod.	Mod.	.....	Mod.	.....	2	1,000	Postoperative ligation of the vena cava which developed subsequent stasic dermatitis and ulceration; subjective improvement of congestive pain.
18.	A.V.	25	F	2 yrs.	R. leg	Mod.	Marked	.....	.....	.....	Mod.	2	1,000	Pain persists; subjectively the leg is improved as regards heaviness and ease of fatigue.
19.	A.F.	54	F	8 mos.	R. leg	Mod.	Marked	.....	.....	.....	.....	5	2,500	Pain persisted, but there was subsidence of edema; onset of swelling, followed high saphenous ligation.
20.	C.N.	43	M	3 yrs.	R. leg	Min.	Mod.	.....	.....	.....	.....	4	2,000	Symptomatic relief and subsidence of superficial phlebitis (Buerger's disease).
21.	L.S.	51	F	1 yr.	L. leg	Min.	Mod.	Marked	Marked	Mod.	Mod.	2	400	Symptomatic relief and relief of vasospasm.

Of the 21 cases in Table VIII, the duration of symptoms varied from one day to several years. The vast majority of these patients had chronic thrombophlebitis. An average of seven autonomic blocks was given to this group of patients, the usual intravenous dose ranging from 250–500 mg. This therapy, for the most part, was given periodically.

UNDESIRABLE REACTIONS TO TETRA-ETHYL-AMMONIUM

The administration of tetra-ethyl-ammonium in dosages of 500 mg., or less, has not been accompanied by any serious toxic effects in more than 1,500 injections. One patient has received 42,000 mg. over a period of six weeks without unfavorable sequelae. Caution must be exercised in giving this drug to certain types of patients however. Hypertensive patients, particularly those in whom a neurogenic component of the hypertension has been identified or suspected, should have great care exercised during administration. Precipitous drops in blood pressure have been encountered in these patients, the systolic pressure falling as low as 50 mm. of mercury. Nausea, vomiting, sweating, pallor, and temporary peripheral circulatory collapse are concomitant with this marked fall in pressure. Nonhypertensive patients, in whom it is reasonable to anticipate an overly-labile sympathetic nervous system, should also have the drug administered with caution. Elderly patients, as a rule, do not tolerate tetra-ethyl-ammonium as well as the younger age-groups. It is advisable, in older individuals, to start with small dosages and gradually work up to 500 mg. over a period of a few days. Undesirable falls in blood pressure may be quickly and effectively countered by a moderate Trendelenberg position and injection of a few minims of epinephrine.

A state of dyspnea similar to that observed in hysterical hyperventilation has developed in some patients immediately after injection of tetra-ethyl-ammonium. In a few patients the sensation of weakness, fatigue and lightheadedness was very pronounced. They appear to experience difficulty with muscle movement, though when tested there was no loss of strength or change in reflexes.

A delayed drop in blood pressure has been observed in certain patients, usually in the older age-group, who, after partial return to normal of the initial drop in pressure, apparently lose their compensating mechanisms defending blood pressure and a secondary drop in pressure takes place which may be greater than the primary fall. Again, undesirable falls in blood pressure may be countered by the above measures.

Some patients treated daily over a long period of time, develop a mild degree of myasthenia and lassitude that disappears with cessation of administration of the drug. Occasionally, a patient has noted difficulty in urination during active treatment, especially when intramuscular injection has been employed. It is, of course, inadvisable to administer tetra-ethyl-ammonium in anuric states as its excretion is largely dependent upon adequate renal function.

In small patients a 500 mg. I. V. injection may be followed by fasciculation of muscles. This is probably evidence of over-dosage. Large intramuscular doses in obese people may produce the same effect which may last for several hours. No ill effects have been noted from this phenomena.

DISCUSSION.—Autonomic blockade, in a patient with vascular disease or related disorders, which produces alleviation of pain or amelioration of the clinical picture, may produce such an effect by means other than relief of vasospasm alone. The exact mechanism involved in unknown. It is postulated by the authors that many of the results observed in the several series of cases reported in this paper might best be explained upon the basis of altered tissue metabolism secondary to sympathetic block or sympathectomy, realizing, of course, that in certain cases, altered blood flow secondary to the procedures mentioned might, in turn, produce desirable alterations in tissue metabolism which were in turn reflected as modifications or improvement in the clinical picture. Such a postulation was primarily necessitated by numerous observations of marked symptomatic improvement occurring in patients with vascular disease in whom vasodilatation was not produced by autonomic blockade. The possibility of a viscious reflex arc being interrupted by ganglionic block with subsequent modification of the pain mechanism must of course be given due consideration. If such actually occurs, it still leaves unexplained the duration of relief of symptoms far-outlasting the expected duration of the block. This frequently seen phenomena, again, suggests modified tissue metabolism of an unknown nature. It is also possible that certain afferent pathways (if such exist) in the autonomic nervous system may be blocked by the injection of tetra-ethyl-ammonium and, thus, contribute to the relief of painful symptoms.

SUMMARY

1. The administration of tetra-ethyl-ammonium for the production of autonomic blockade has proven of value in diminishing or relieving in severity the pain of causalgia, posttraumatic painful states, herpes zoster, Buerger's disease and thrombophlebitis. The improvement following such therapy has been sustained in certain cases.

2. The drug has proven to be a satisfactory implement for clinical investigation and therapy in the conditions reported.

3. The occurrence of certain undesirable side-effects following the administration of tetra-ethyl-ammonium in some cases necessitates the institution of certain precautions during its administration.

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DISCUSSION.—DR. WILLARD BARTLETT, St. Louis, Mo.: I should like to ask the duration of the effect, and how frequently injections are needed.

DR. MICHAEL E. DEBAKEY, New Orleans, La.: At the present time Drs. Thorpe Ray, George E. Burch, and I are engaged at the Tulane University School of Medicine in a study of vascular responses to tetra-ethyl-ammonium bromide, in an effort to evaluate its practical usefulness in peripheral vascular problems. The physiologic and clinical aspects of these studies will be described later. The observations upon which the following comments are based are not considered sufficiently extensive to permit a final evaluation of this agent, but the great interest manifested in its use, the consistency of the data, and the definite differences between our findings and those of other observers prompt this preliminary report.

In addition to clinical observations, objective studies have been made of the peripheral vascular response to tetra-ethyl-ammonium bromide by means of plethysmographic and thermometric measurements on normal subjects and on patients with peripheral vascular disease. These studies were made under controlled atmospheric conditions, after the intravenous administration of 300 to 500 mg. of tetra-ethyl-ammonium bromide, first under resting conditions and then following local nerve and regional sympathetic block.

As will be noted from the graphs presented, the clinical or general systemic reactions to the drug were essentially similar to those reported by others, though much less pronounced and of much shorter duration. The plethysmographic and thermometric data, however, were quite different. Following the administration of tetra-ethyl-ammonium bromide there was a variable response in skin temperature as determined at 11 to 20 different areas, varying from no response at all in some instances to a maximum rise of

4° C. in others. In a few areas there was an actual decrease in the skin temperature. If an elevation occurred, it did not persist more than 15 minutes in any case.

After a return to the basal vascular status, local nerve and regional sympathetic block invariably produced an increase in the skin temperature from two to six times greater than the increase caused by tetra-ethyl-ammonium bromide. Of particular significance is the fact that local nerve or regional sympathetic block invariably resulted in an increase in skin temperature in areas which had failed to respond to the use of the drug. Finally, the duration of the elevation following local nerve or regional sympathetic block was in every instance considerably more prolonged than the elevation following the use of the drug.

Measurements by plethysmography, which is an extremely sensitive and rapid method of study, were made simultaneously with the thermometric determinations and invariably corroborated the thermometric observations for the tips of the fingers and toes. The percentage change, in fact, was shown to be even greater, and it occurred without any lag.

We have no explanation for the distinct differences between these results and those reported by others. On the basis of our own observations, however, it seems unlikely that tetra-ethyl-ammonium bromide will prove of great value, either diagnostically or therapeutically, in peripheral vascular disease.

DR. DANIEL C. ELKIN, Emory University, Ga.: An investigation of the use of tetra-ethyl-ammonium bromide in cases of acute arterial injuries has been progressing in the surgical laboratory of Emory University Medical School under the direction of Drs. F. W. Cooper, Jr., and R. L. Robertson. The method has consisted of excising the trifurcation and terminal portion of the aorta in dogs. At the time of operation and postoperatively the dogs received a varying number (six to nine) of injections of tetra-ethyl-ammonium bromide in the amount of 25 mg. per kilogram of body weight.

It has been previously shown by Brooks, Leriche and others that excision of the bifurcation of the aorta without sympathectomy will result in swelling, paralysis, gangrene and death in the majority of animals. A group of control animals was run with confirmation of these findings in every instance. Ten animals have been similarly operated upon, but in addition received tetra-ethyl-ammonium bromide. None of these animals developed swelling, ulcerations or gangrene of the posterior extremities. A transient weakness was present in all instances, but in the dogs which survived this cleared within four days. Through technical error the intramuscular injections were given in the posterior extremity in one instance, with the formation of an abscess, and with the dog dying on the 9th postoperative day as a result of extensive suppuration.

The marked clinical improvement in the nine animals which survived with rapidly increasing tolerance for activity, suggests that tetra-ethyl-ammonium bromide may be a valuable adjunct in the treatment of acute arterial injuries of major vessels.

DR. R. L. BERRY, Ann Arbor, Mich.: In reply to Doctor Bartlett's question, the block reached a maximum height between 20 and 30 minutes, and gradually tapered-off to depletion usually in 60 to 80 minutes, as manifested by thermacouple response.

DR. FREDERICK A. COLLER, Ann Arbor, Mich. (closing): I want to thank Doctors DeBakey and Elkin for their discussion. I think there can be no doubt about the pharmaceutic action of the drug that has been carefully worked out by Doctor Acheson and Doctor Moe, and their associates.

The observations of Doctor DeBakey that tetra-ethyl-ammonium bromide does not cause the degree of vasodilation produced by lumbar block is interesting, but not at all in accord with our observations, which have been many. I shall await with interest to learn of his further experiences with this chemical.

There is so much that we do not yet know about the autonomic nervous system, but we feel that this chemical method of study may be helpful in adding to our knowledge of that system, as well as offering a new therapeutic measure for the relief of unpleasant symptoms associated with its disorders.

WOUNDS OF THE LIVER*

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LIVER WOUNDS occur with such frequency and severity that they may be considered the major problem in abdominal injuries. Fox[1] reviewed 270 thoraco-abdominal wounds seen in an American hospital in Italy, and reported a 57 per cent involvement of the liver. In approximately 10 per cent of these there was an associated injury of other viscera. The over-all mortality rate for wounds of the liver was 27 per cent in 829 patients, according to Madding.[2]

The liver, the largest organ in the body, is extremely vulnerable to penetrations of both lower chest and upper abdomen. It should be emphasized that the liver is an organ with multiple functions and that as the result of trauma various manifestations occur which may or may not be related to the severity of the trauma. Experimental removal[3] of as much as 50 per cent of hepatic tissue can be performed without serious impairment of function. It has been demonstrated that the liver has remarkable regenerative and recuperative power.[4] In dogs, as much as 90 per cent of the liver can be removed at successive intervals with survival of the animal, and, following massive blood loss,[5] the functional reserve has been shown to be unimpaired.

Trauma of the liver may be classified as direct and indirect. The former results chiefly from penetrating missiles, with the varying factors of size, velocity and direction. The magnitude of injury is primarily dependent upon the explosive effect of the missile, rather than its size. In these, the wound of entrance is much larger than that of exit. The lacerations are stellate and the tissue involvement is not confined to the area immediately surrounding the path of the projectile, but at a considerable distance, as seen in wounds of muscle. There is an associated vascular damage in the form of tears of large vessels, moderate to massive hemorrhage and severance of normal blood supply, producing further devitalization, necrosis and subsequent infection. The main hepatic vessels and bile ducts are rarely involved because of their protected position on the inferior surface. Following injury, there is usually profuse hemorrhage from the torn surface, along with drainage of bile from the interrupted ducts. In penetrating wounds of the lower thorax, the dome of the liver is most frequently involved, and the right more than the left. With such an associated wound of the diaphragm, extravasated blood and bile may find access to the pleural space and result in biliary empyema.

As opposed to direct trauma, nonpenetrating wounds have a lesser incidence, but may present identical pathologic findings, complications and outcome. Shedden and Johnson[6] have classified this group according to the

* Read before the 58th Annual Session of the Southern Surgical Association, Hot Springs, Va., December 12, 1946.

degrees of involvement and severity: (1) a rupture of liver tissue with simple laceration of Glisson's capsule represents minimal trauma; (2) separation of the capsule by subcapsular hemorrhage and damage to underlying structures occasionally occurs; (3) a central rupture with hemorrhage into the parenchyma can develop with possible later abscess formation. This classification does not take into account the size and depth of the wound, or degree of involvement of total tissue—factors which are of much value in prognosis.

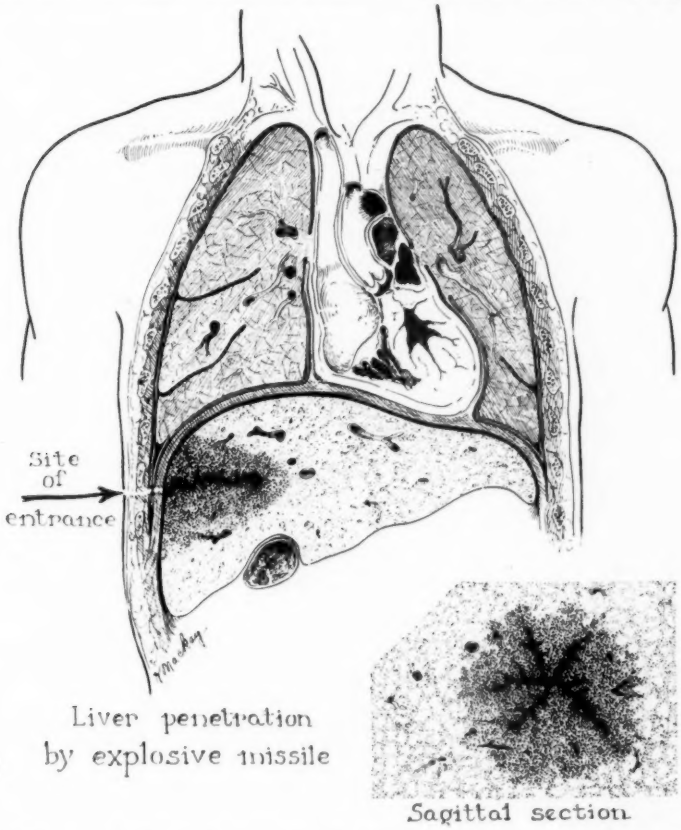


FIG. 1.—Diagram demonstrating the destruction of liver tissue well away from the missile tract.

In both direct and indirect trauma the pathologic findings are similar. Following cessation of hemorrhage from opened vascular channels, there remains a drainage from the biliary system, proportional to the amount of injury. Repair must be effected, first by a removal of devitalized and necrotic tissue, and later by regeneration of the structures destroyed. During tissue autolysis, vascular and biliary tracts may be further opened, and secondary hemorrhage and extravasation of bile occur.

Liver wounds may produce marked systemic manifestations, often out of proportion to the degree of injury. During the period immediately following injury, shock may be profound and not always equivalent to blood loss.

Following recovery from this initial period, secondary manifestations appear. These are concerned mainly with blood loss, biliary extravasation, hepatocellular damage, and occasionally associated renal dysfunction. The signs and symptoms of acute anemia may be seen, along with those of intraperitoneal hemorrhage. Bile peritonitis and empyema may now become manifest. Hepatocellular damage is demonstrated in a number of ways, each relating to a particular function performed by liver cells. The presence of jaundice is usually manifested late, of slight degree and transient. Interference with the deaminization of amino acids and the proper utilization of glycogen may be shown by lowered blood protein and an abnormal carbohydrate tolerance. Fibrinogen formation may be deficient and prothrombin may drop to a critically low level and thereby increase the clotting time of the blood.

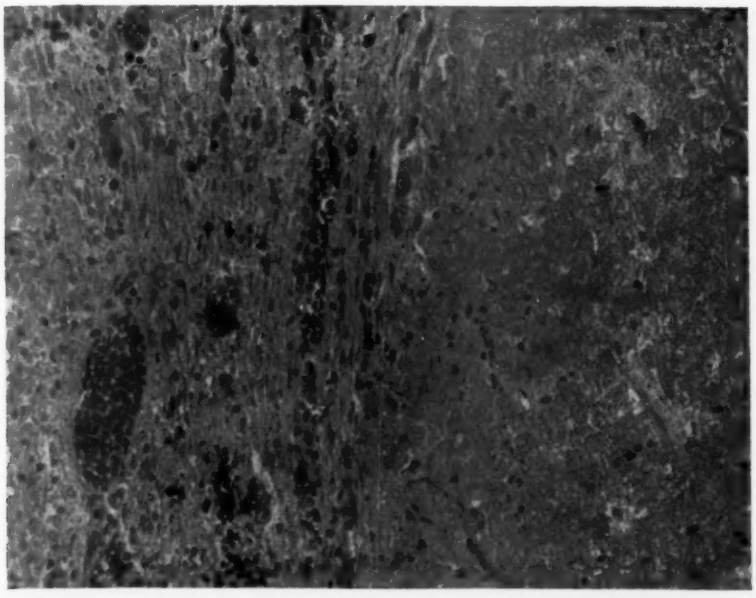
The most serious complication of liver trauma is the occurrence of the so-called hepatorenal syndrome, which more often follows extensive crushing trauma than penetrating wounds. Hyperpyrexia develops, the pulse becomes weak and rapid, extreme restlessness is manifest, and often delirium and collapse supervene, followed in some cases by death. Oliguria is first seen with red blood cells, casts and albumin in varying amounts, and may be succeeded by anuria. Nonprotein nitrogen and creatinine progressively increase in blood concentration. Blood sugar, cholesterol and plasma chlorides are usually unaltered. In the presence of anuria, retention of fixed acids occurs, leading to a depletion of alkali reserve and a lowered carbon dioxide combining power.

The nature of the hepatorenal syndrome has not been satisfactorily determined. In many ways it is analogous to the "crush syndrome" seen following trauma to extremities. Orr and Helwig[7, 8] thought it to be due to the effect on the kidney of a soluble toxin produced by necrosis of the liver. Boyce[9] is of the opinion that a toxin may be produced in necrotic liver tissue, but that the renal damage is due to "an increase of its normal detoxifying duties, which are increased by failure of the detoxifying function of the liver rather than by any specific action of the toxin." Coller[7] suggested a possible explanation on the basis of alterations of physiologic processes such as are produced by shock, hypotension, dehydration, alkalosis, and hyoproteinemia. Massive damage is a prerequisite for the appearance of this complication. Boyce and McFetridge[9] have experimentally produced this condition in dogs by heterogenous liver implants in the peritoneal cavity. These results, and others,[10] point to the emphasis to be placed on attempting to remove all damaged liver tissue which is definitely necrotic and may precipitate such a reaction.

EXPERIMENTAL CONSIDERATIONS

Clinically, it is desirable to ascertain whenever possible the degree of functional impairment of the liver following injury. This affords some index as to indicated treatment and prognosis. To demonstrate any correlation that might exist between the proven extent of liver damage and the results of easily applied clinical tests, the following experiments were undertaken:

FIG. 2



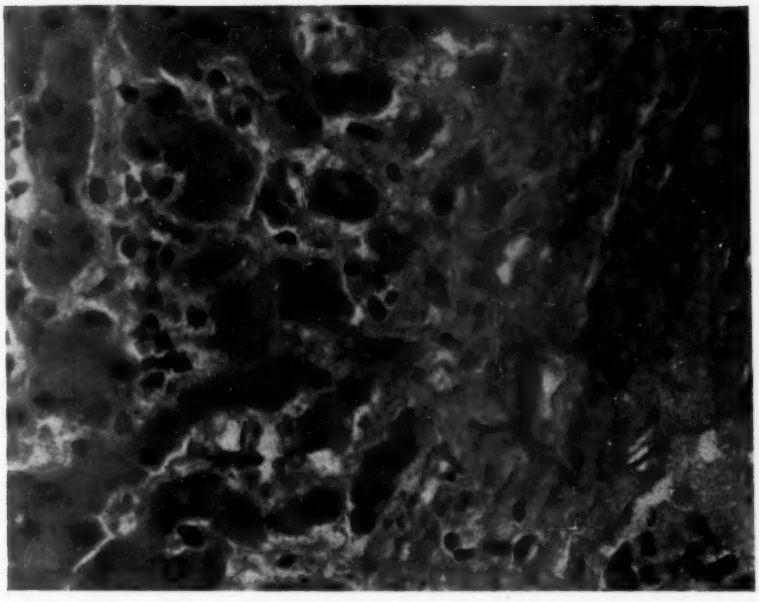


FIG. 3

FIG. 2.—Photomicrograph of penetrating wound of the liver of a patient, showing area of infarction and the surrounding inflammatory reaction, with infiltration of leukocytes and fibrosis.

FIG. 3.—Photomicrograph of liver of patient showing disruption of the liver cords with fibroplasia away from the site of injury.

A group of dogs, weighing 10 to 20 kilograms each, was selected. Control determinations were made on the intact animals, for galactose tolerance, bromsulfathalein excretion, alkaline phosphatase activity in serum and prothrombin time. In the case of the first two, the intravenous methods were employed. All tests are those described in standard texts.

The dogs were given intravenous pentobarbital sodium in dosages of 64 milligrams for each five pounds body weight. Control determinations were

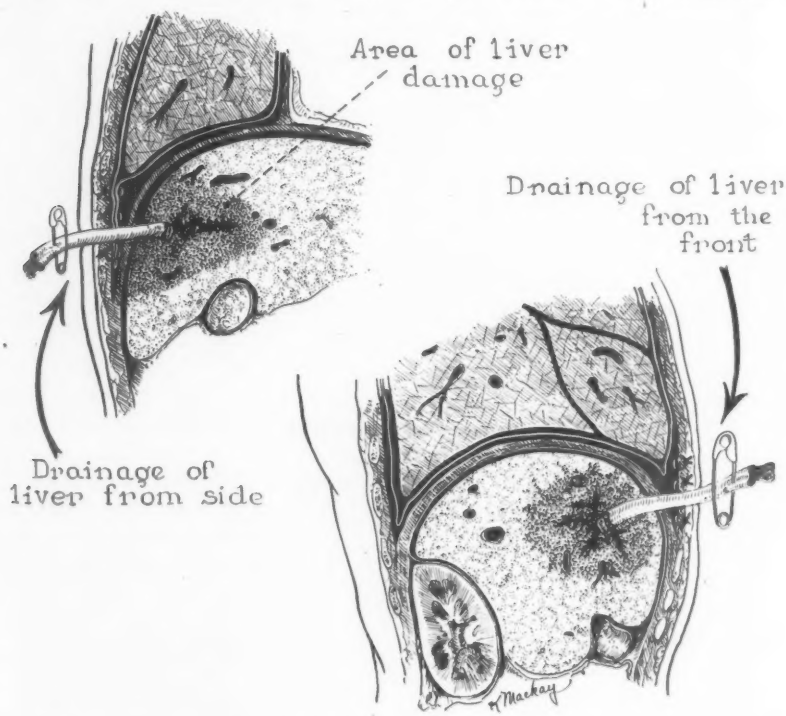


FIG. 4.—Drawing representing the method of drainage when the wound is high and lateral. The diaphragm has been fixed to the chest wall, closing-off the pleural cavity. A direct approach may be made to the area of damage, near the dome of the liver. The location of the drain is shown when the damage is anterior and superior.

again performed, and no appreciable differences were noted between intact unanesthesized animals and those under anesthesia.

Dogs were then selected in pairs, anesthesia induced, celiotomy performed, and the liver exposed. Varying amounts of liver were subjected to manual trauma, rapidly striking the individual lobes approximately fifty times. This produced evidence of considerable damage, as shown by minor tears in Glisson's capsule, subcapsular hemorrhage, external hemorrhage. In some animals it was estimated that 50 per cent of the liver tissue had been damaged, and in others this percentage was higher, all the lobes having been traumatized. The abdomens were then closed. All the animals survived this procedure. In some there was a moderate degree of postoperative shock, which

was treated with intravenous infusions of physiologic saline, with good response.

One hour after trauma, the various clinical determinations were again made, blood samples being drawn at intervals of 30 minutes for one and one-half hours. The results, as well as the control curves, are shown in the accompanying diagrams.

At the end of six days some of the animals were again given an anesthetic and samples of blood drawn for the determinations. The abdomens were then opened and the livers examined, specimens were taken for histopathologic study. Grossly, the surface of the liver in most instances had become covered by omentum, particularly in those which had superficial capsular tears on the anterior and inferior surfaces. Areas of infarction and yellow necrosis were evident.

It was remarkable that following the initial period of shock and recovery from the anesthetic, the animals showed little evidence of being ill, ate heartily, were alert and would exercise when given the opportunity.

The conclusions that may be drawn from this preliminary report of the work in progress center chiefly about the obvious fact that the liver has a very large functional reserve, as well as tremendous recuperative and regenerative powers.

TREATMENT

In rupture of solid viscera, particularly the liver and spleen, treatment revolves about control of hemorrhage. This can be easily effected in the spleen by its removal. The liver, however, is such a friable organ that it can be seldom sutured. Approximation of the edges by sutures which are tight enough to prevent hemorrhage from the damaged surfaces will result in cutting of the tissues. However, with minimal wounds near the periphery, sutures may occasionally be used advantageously. Whenever damaged tissues are placed in apposition, the processes of repair are delayed, necrosis and sloughing must occur before union is complete.

Hemorrhage is controlled in most instances by packing. The possibility of infection is increased by this procedure and after removal, secondary hemorrhage may occur and necessitate repacking. A liver which has been too tightly packed may develop pressure necrosis. When wounds are extensive and located in inaccessible positions, particularly beneath the diaphragm, the control of hemorrhage becomes difficult. As a rule, packing is brought out through a separate stab wound; it is sometimes necessary to re-enter this wound and compress the area from which hemorrhage occurs.

Recently, several new materials have shown promise as hemostatic agents.[11, 12] Among these are oxidized cellulose, fibrin and gelatin foam. An ideal material should control bleeding, act as a drain, and undergo absorption within a safe period as regeneration of liver tissue takes place.

Muscle grafts, in many instances, are beneficial, but with extensive damage it is not always feasible to place a sufficiently large section of muscle over the area of hemorrhage. The chief disadvantage of muscle graft is its inability to

FIG. 5

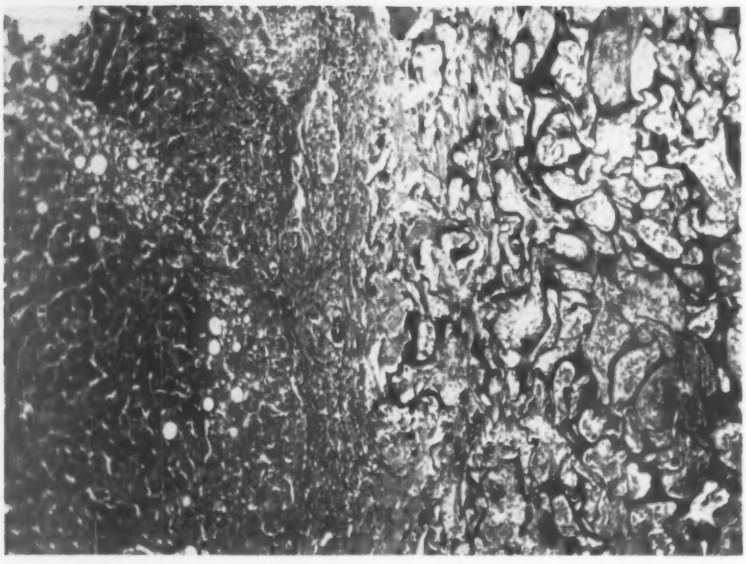


FIG. 6

FIG. 5.—Photomicrograph demonstrating healing process and the formation of fibrous tissue after a laceration of the liver in the dog, without traumatizing the underlying structures.

FIG. 6.—Photomicrograph demonstrating healing of a liver in which gelatin foam has been placed into preformed tract into the substance of the liver. The formation of fibrous tissue and the development of new blood vessels and infiltration with leukocytes are demonstrated in the trabeculae of the gelatin foam.

become fixed and remain so for any length of time. On damaged liver it will not adhere and healing does not occur until the necrotic tissue is removed.

Fibrin foam can be successfully used for the control of hemorrhage from the liver surface. It is most effective in wounds in which there is mild oozing

FIG. 7-A.—Photomicrograph of the liver of a dog traumatized two weeks before. There is marked evidence of necrosis, fatty degeneration and leukocytic infiltration. The greatest evidence of necrosis occurs near the surface at the site of the trauma.

DOG #1	RETENTION EXCRETION AFTER 30 MINUTES	ALKALINE PHOSPHATASE	GALACTOSE TOLERANCE 30, 60, 90, MINUTES AFTER INJECTION	PROTHROMBIN TIME
TRAUMA	PER CENT	UNITS	MG %	SECONDS
BEFORE	10%	6.7	124 – 69 – 0	18
AFTER				
1 HR.	25%	12.9	94 – 31 – 0	21
24 HRS.	20%	10.3	38 – 18 – 0	19
1 MO.	15%	9.1	34 – 15 – 9	20

FIG. 7-B.—Chart representing functions before trauma to the liver of a dog (as shown in Fig. 7-A) and the results at various intervals afterwards. It is noted that there is no appreciable reduction in these functions following trauma.

from a cut-surface. Its use in this respect represents the ideal type of pack when placed on a surface with a minimum of damaged tissue, and close adherence is obtained. Unfortunately, the majority of wounds of the liver do not present this type of bleeding.

Jenkins[11] has shown that gel foam (bovine thrombin incorporated in a gelatin matrix), used on a cut-liver surface, accomplishes excellent hemostasis. Absorption is effected in the presence of leukocytes. This substance is

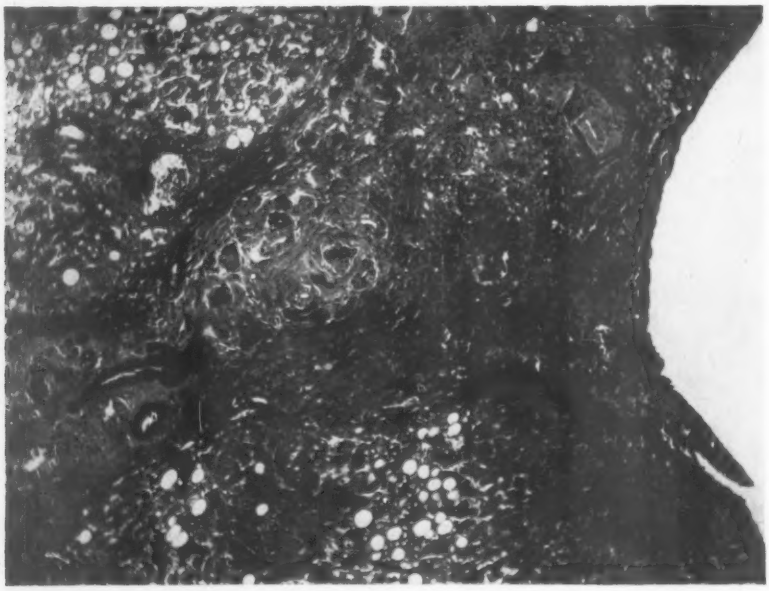


FIG. 8-A.—Photomicrograph of a liver of a dog which was traumatized three weeks before sections were made. There is still evidence of marked destruction well away from the site of the trauma in the substance of the liver, with moderate fatty infiltration and leukocytic infiltration.

DOG #4

TRAUMA	RETENTION EXCRETION AFTER 30 MINUTES	ALKALINE PHOSPHATASE	GALACTOSE TOLERANCE 30, 60, 90, MINUTES AFTER INJECTION	PROTHROMBIN TIME
	PER CENT	UNITS	MG %	SECONDS
BEFORE	3 %	13.9	50-26-0	22
AFTER 1 HR.	15 %	12.4	31- 6-0	20
1 MO.	8 %	11.2	31-20-9	22

FIG. 8-B.—Chart representing results of functional tests of liver of dog (Fig. 8-A) before and after direct trauma to the liver. It is noted, as in previous dogs, that no appreciable change is denoted after the liver had been directly traumatized.

promising, but as yet there is no ideal material for the control of hemorrhage from the traumatized liver.

In the repair of liver wounds it is essential to close carefully all openings in the diaphragm. This has a dual purpose: (a) to restore the integrity of the abdominal and thoracic cavities and prevent the passage of bile and blood

into the pleural sac, where it is tolerated less than in the peritoneal cavity, (b) to restore the mechanics of the respiratory system and prevent the formation of a diaphragmatic hernia.

Inasmuch as the extent of cellular damage is greatly beyond the actual tract of the projectile, the ideal procedure would be primary débridement of the nonviable tissue. It is difficult to estimate the extent of damage at the time of operation. However, if this could be determined and the devitalized tissues removed, healing could then occur without sloughing and infection. A disadvantage of débridement is the hemorrhage which accompanies it. With the advent of a better substance for controlling hemorrhage, primary débridement could then be performed in the same manner as it is now done in other tissues.

At the present time, drainage of liver wounds must always be carried out to control bleeding and to allow escape of bile, blood and the products of infection and tissue necrosis. As mentioned before, drains should be brought out through a separate stab incision, most advantageously placed beneath the costal margin. Drainage by way of the transthoracic route is obviously not tenable. Drains should not be placed in the celiotomy incision because this favors herniation of the omentum and increases the likelihood of wound dehiscence. The wound of entrance or exit may at times be employed for drainage, provided there is no communication with the pleural space and dependency is assured. With lateral wounds of the diaphragm, following firm closure by suturing of this muscle to the anterolateral thoracic wall, drains may be placed directly to the site of the wound. The wound in the chest wall is excised, and the overlying ribs are removed to allow a direct approach to the liver.

The period of drainage cannot be arbitrarily set. If drains are satisfactorily placed and the control of hemorrhage is accomplished during the first hours or days, the tendency is to remove the drain too early. If it functions as both a drain and a pack there will be a minimal bleeding and drainage of bile. The drains may become adherent and cause secondary hemorrhage upon removal. Gradual removal over a period of days is more satisfactory. When the wound is of sufficient size and the peritoneal cavity well-sealed, it may be necessary to reinsert a drain to allow continued escape of bile. During the process of subsequent healing a large amount of tissue slough and bile drainage will take place. Healing will not occur until full sequestration of the destroyed tissue takes place and fibrosis occurs. If the wound is allowed to close or is blocked by too large a drain, bile accumulates, infection follows, and may lead to the formation of an abscess within, above or below the liver.

The general care of wounds of the liver are of paramount importance throughout the course following injury. During the first phase attention is directed towards fluid replacement and correction of the hemorrhage and shock. Surgery should not be undertaken until full response has been made, but there occasionally exists protracted failure to respond to blood replacement and immediate operation to control the continued bleeding is necessary

in spite of the existent shock. The general postoperative care must be instituted in addition to maintenance of fluid balance, protein equilibrium and a correction of vitamin deficiences. The factors which govern systemic therapy are mainly the degree and the type of injury and the complications.

SUMMARY

1. Wounds of the liver constitute one of the major problems of abdominal injuries.

2. The manifestations depend on the indirect and direct forms of trauma.

3. The pathologic effects are similar in each and are proportional to the degree of initial trauma and subsequent complications.

4. Clinical manifestations are presented in the form of hemorrhage, shock, renal insufficiency and infections.

5. Following trauma, the liver has a remarkable recuperative power.

6. If large amounts of tissue are devitalized, repair will be delayed until full sequestration occurs. This process further increases the likelihood of hemorrhage and escape of bile.

7. There is evidence to suggest that in the dog, the usual functional tests are not greatly affected following massive trauma to the liver.

8. The complications are for the most part proportional to the degree of involvement, subsequent interference with blood supply and associated infection.

9. It is felt that when materials for control of hemorrhage are perfected, primary débridement of the damaged liver should be performed, as in wounds of soft tissues.

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DISCUSSION.—DR. T. C. DAVISON, Atlanta, Ga.: I just want to stress one point. I have observed not only in civilian practice but in an Evacuation Hospital, in France, in 1918, that any penetrating wound of the chest below the nipple line, particularly on the right side, is apt to injure the liver. We reached the point where we always explored the abdomen in such cases, particularly if there was no site of exit, because nobody knew where that missile had gone. Roentgenograms would locate the foreign body but did not show what organs had been damaged—the dome of the liver, the stomach, the kidneys, the spleen, the intestines, and sometimes the spinal cord. I just want to say that in such wounds exploration is advisable.

DR. MICHAEL E. DEBAKEY, New Orleans, La.: Doctor Davison's mention of wounds of the liver in World War I prompts me to present some statistical data on similar wounds in World War II, based upon records and analyses made available to the Office of the Surgeon-General. Many of these data were recorded by the Second Auxiliary Surgical Group, which had an extensive experience in the Mediterranean Theater of Operations.

Abdominal injuries in World War II comprised approximately 6 per cent of all wounds, and wounds of the liver comprised about 25 per cent of all abdominal wounds. In World War I wounds of the liver comprised 13 per cent of all abdominal wounds, which is about half of the World War II incidence. Uncomplicated hepatic injuries, that is, liver injuries not associated with injuries to other viscera, constituted about 40 per cent of the total wounds of the liver in World War II, and complicated wounds constituted about 60 per cent. In World War I these respective percentages were 75 and 25. It will be observed from the comparative figures that there is a significantly higher total incidence of hepatic injuries in World War II, and an increase in the ratio of complicated to uncomplicated injuries. The conclusion seems justified that in World War II a larger proportion of severely wounded men were observed before death and were submitted to surgery.

Of particular interest from the standpoint of prognosis in World War II is the so-called multiplicity factor, which refers to the number of abdominal organs injured in a given case, as determined at operation. The case-fatality rate calculated on this basis increased in almost direct proportion to the number of viscera injured. For uncomplicated wounds of the liver the case-fatality rate was about 10 per cent; when one other viscus was injured, it was about 28 per cent; when two other organs were injured, it was almost 40 per cent; when three others were injured, it was almost 55 per cent; when four others were injured, it was about 85 per cent. According to the Second Auxiliary Surgical Group, which provided perhaps the best available statistics on the subject for World War II, the total mortality for wounds of the liver in that war was 27 per cent, which is a very distinct improvement over the World War I figure of 66 per cent.

As to treatment of wounds of the liver, experience proved that the best results were secured by the establishment of adequate external drainage of bile and the products of traumatized tissue. Early in the war dry packs were frequently used, but the results were not good and eventually this method was entirely discarded.

According to the statistics of the Second Auxiliary Surgical Group, shock was the cause of death in something over half of the fatal hepatic injuries. Pulmonary complications were responsible for the fatalities in about 17 per cent of the cases and peritonitis in about 12 per cent. Oliguria and renal failure were present in 8.5 per cent of the deaths, and the question was raised of the possible relationship of liver damage to renal failure; the so-called transfusion or shock kidney, however, could not always be excluded. The remaining proportion of fatalities was attributable to various miscellaneous causes, which were not always connected with the hepatic injury. The most frequent complication of hepatic wounds was subphrenic abscess, with biliary empyema and intrahepatic abscess next in order of frequency. Complications could often be traced to inadequate drainage.

WOUND DISRUPTION AND EARLY AMBULATION*

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EARLY AMBULATION is a valuable method in the management of postoperative patients. Based on sound physiologic principles, it not only reduces the incidence of vascular and pulmonary complications, but appreciably shortens convalescence. These clear-cut results have won it many advocates. Nevertheless, there is still a certain deep-rooted scepticism concerning the danger of wound disruption. This is the greatest deterrent to the general acceptance of the method. In the hope of clarifying this point, it is the purpose of this paper to present a study of the disruptions of abdominal wounds in patients treated at conventional bed rest and in those subjected to early rising.

The importance and frequency of wound disruption as a surgical complication have been extensively discussed in the surgical literature. Excellent reviews are at hand in the articles of Singleton and Blocker,[1] Glenn and Moore,[2] Fallis,[3] and Jenkins,[4] as well as a host of others. The incidence of disruption varies from 0 in 16,456 celiotomies by Baldwin[5] to 1.8 per cent by Kraybill.[6] The average is about 0.6 per cent. Upper abdominal operations are somewhat more prone to disruption than lower abdominal ones. Glenn and Moore[2] report 0.92 per cent for biliary tract operations, 1.55 per cent for stomach operations, and 1.96 per cent for large bowel operations. In gynecologic work, Schmitz and Beaton[7] report 0.15 per cent, and Hesseltine and Bohlender[8] 0.442 per cent. The mortality of disruption varies from 32 per cent to 68.7 per cent.

Three groups of cases have been selected for this study. In one group are included 856 abdominal cases operated upon at St. Thomas Hospital between January 1, 1946 and July 31, 1946. The great majority of these were treated in the conventional manner.

In the second group are 1908 celiotomies observed at the Brooke General Hospital. All were subjected to early ambulation, unless specifically contraindicated. These have been previously reported in part.[9] Since the majority of patients in the Brooke series were healthy young soldiers, the two are not exactly comparable. However, there is some similarity, as included are a very sizable number of women, veterans, retired personnel and children. To provide more comparable data, a small series of 138 recent private cases are added. All were personally operated upon and followed.

In the St. Thomas series (Table I), there were 856 celiotomies with subsequent abdominal wound disruption in nine, or 1.05 per cent, of the incisions. Seven hundred and twenty-six, or 84.81 per cent, of the incisions were in the

* Read before the 58th Annual Session of the Southern Surgical Association, Hot Springs, Va., December 12, 1946.

TABLE I

LAPAROTOMIES AT ST. THOMAS HOSPITAL — JAN. 1, 1946 TO JULY 31, 1946

TOTAL	DISRUPTIONS	%
856	9	1.05

ABDOMINAL INCISIONS

TYPE OF INCISION	NO.	%	DISRUPTIONS	%
LOWER ABDOMINAL	726	84.81	3	0.41
UPPER ABDOMINAL	129	15.19	6	4.65

UPPER ABDOMINAL INCISIONS

TYPE	NO.	%	DISRUPTIONS	%
VERTICAL	97	75.19	6	6.19
TRANSVERSE	32	24.81	0	0.00

TABLE II

SUTURE MATERIAL IN FASCIAL CLOSURE — UPPER ABDOMINAL

INCISION	SILK AND COTTON	CAT GUT INTERRUPTED	CAT GUT CONTINUOUS	TOTAL
VERTICAL	60	29	9	98
TRANSVERSE	29	1	1	31
TOTAL	89	30	10	129

SUTURE MATERIAL IN PERITONEAL CLOSURE — UPPER ABDOMINAL

INCISION	INTERRUPTED SILK OR COTTON	CONTINUOUS CAT GUT	CONT. CAT GUT REINFORCED
VERTICAL	0	66	31
TRANSVERSE	12	15	5
TOTAL	12	81	36

lower abdomen, with three, or 0.41 per cent, disruptions. One hundred and twenty-nine, or 15.19 per cent, of the incisions were in the upper abdomen, with six, or 4.65 per cent, disruptions. Ninety-seven, or 75 per cent, of all upper abdominal incisions were vertical in type. All six of the upper abdominal wound disruptions occurred in this group of vertical incisions, with a group incidence of 6.19 per cent. In the upper abdominal cases (Table II), the fascia was closed with interrupted silk or cotton in 89, with interrupted catgut in 30, and with continuous catgut in ten. The peritoneal closure was with interrupted silk or cotton in 12, continuous catgut in 81, and continuous catgut reinforced with silk or cotton in 36. In the upper abdominal disruptions (Table

TABLE III

CLOSURE IN UPPER ABDOMINAL DISRUPTIONS

	SILK AND COTTON	CAT GUT INTERRUPTED	CAT GUT CONTINUOUS
FASCIA	4	2	0

	INTERRUPTED SILK AND COTTON	CAT GUT CONTINUOUS REINFORCED	CAT GUT CONTINUOUS
PERITONEUM	0	1	5

UPPER ABDOMINAL DISRUPTIONS

PERITONEAL CLOSURE WITH CONTINUOUS CAT GUT		
81 CASES	5 DISRUPTIONS	6.1%

PERITONEAL CLOSURE WITH INTERRUPTED COTTON AND SILK OR CONTINUOUS CAT GUT REINFORCED WITH INTERRUPTED COTTON AND SILK		
48 CASES	1 DISRUPTION	2.08%

III), the fascia was closed with interrupted silk or cotton in four and interrupted catgut in two, the peritoneal closure in five instances was continuous catgut, and, in one, continuous catgut reinforced with interrupted silk. There were five, or 6.17 per cent, disruptions in the 81 upper abdominal cases in which the peritoneum was closed with continuous catgut and only one, or 2.08 per cent, in the group of 48, in which the peritoneum was closed entirely with interrupted cotton or silk, or in which the continuous catgut was reinforced with interrupted cotton or silk. The diagnoses in the cases disrupting, and the operations performed are shown in Table IV.

Five of the nine cases of disruption occurred following operations on the stomach, and four of the nine were in individuals suffering from malignant disease. In two instances, the disruptions were treated by strapping the wounds. In one, through-and-through sutures of silkworm gut were utilized, while in the other six, the closure was in layers. Three of these were reinforced by through-and-through sutures. Two patients died—a mortality of 22.2 per cent.

In the Brooke General Hospital series, there were 1,908 representative abdominal cases, excluding hernia. There was but one disruption following one

of the 83 operations on the biliary tree. In this case, the incision was a right-Singleton, the fascia was closed with interrupted cotton, and the peritoneum with continuous catgut reinforced with interrupted cotton. The disruption was precipitated by intractable hiccoughs. It did not extend throughout the wound, and was easily handled by strapping. This patient subsequently died as the result of coronary occlusion, bile peritonitis, and pneumonia.

In the Brooke cases, much attention was devoted to wound closure. Interrupted cotton was used for the fascia, and interrupted cotton alone, or reinforced with continuous catgut, was used for the peritoneum. Transverse incisions for upper abdominal wounds were favored by the majority of the

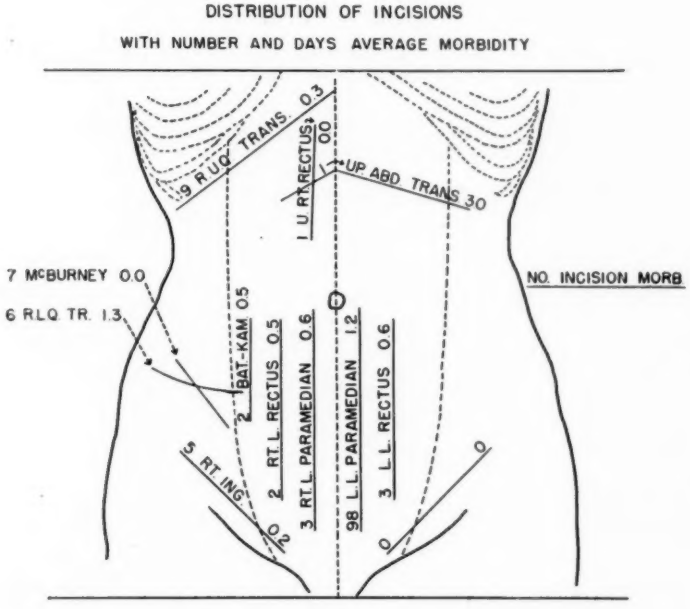

Fig. 1.—138 celiotomies subjected to early ambulation.

operators. However, many of the 90 operations on the stomach and duodenum were performed through vertical incisions. The McBurney incision, or a modification, was used routinely in the 932 appendicectomies. A left paramedian incision was the choice for pelvic operations.

In the 3rd group of 138 private patients, closure was with interrupted cotton through the peritoneum, fascia and skin. The locations of the incisions in the 3rd group of 138 private patients is shown in Figure 1. The figure at the end of the incision represents the number of days the temperature exceeded 100.4° F. Fifty-three per cent of the patients were ambulant on the first postoperative day (Table V), 31 per cent on the second, and 15 per

cent on the third. There were 13 pulmonary complications, no vascular complications, and two wound infections. There is one case listed as a disruption. Actually, there was no dissolution of the suture line, the eventration of the intestine occurring adjacent to a colostomy. In comparing the three groups of cases, it is clear that the incidence of wound disruption is far less in the early risers. This bears out the observation of many authors that wound healing is not impaired by early ambulation. The reports suggest it may be improved.

Ries[10] says: "and I have yet to see the first hernia." Leithauser[11] had no dehiscence or postoperative hernia in 436 cases. In his later report, dehiscence, incisional hernia and recurrences following herniorrhaphy were not more frequent after early rising. There was no instance of eventration in his 900 cases. In 462 abdominal incisions Nelson[12] had three partial disruptions, two of which

TABLE IV

DISRUPTIONS AT ST. THOMAS HOSPITAL JAN. 1, 1946 TO JULY 31, 1946

UPPER ABDOMINAL

DIAGNOSIS	OPERATION
GALL STONES	CHOLECYSTECTOMY
PERFORATED DUODENAL ULCER	CLOSURE
GASTRIC ULCER	GASTROENTEROSTOMY
DUODENAL ULCER	PARTIAL GASTRECTOMY
DUODENAL ULCER	GASTRO-JEJUNOSTOMY
CARCINOMA STOMACH	GASTRO-JEJUNOSTOMY

LOWER ABDOMINAL

DIAGNOSIS	OPERATION
CARCINOMA SIGMOID	RESECTION OF SIGMOID
CARCINOMA BLADDER	URETERO-SIGMOIDOSTOMY
CARCINOMA RECTUM	ABDOMINO-PERINEAL RESECTION OF RECTUM

TABLE V

138 LAPAROTOMIES TREATED BY EARLY AMBULATION

% OF CASES AMBULANT		
1st DAY	2nd DAY	3rd DAY
53.6 %	31.2 %	15.2 %

COMPLICATIONS			
PULMONARY	VASCULAR	DISRUPTIONS	INFECTIONS
13	0	1	2

occurred in patients whose wounds had been closed with catgut, and for whom early ambulation had not been authorized. Powers[13] allowed 39 herniae to rise early, and none recurred. In 39 controls treated by the traditional method of bed rest, there were two recurrences. Ashkins[14] noted one bulging cholecystectomy wound and one weak scar, without protrusion, in 823 cases; Schafer and Dragstedt,[15] in 102 cases, had one eventration and two postoperative herniae. Elman[16] had no wound disruption in 79 cases, but noted three in his control group. Many others testify in the same vein. From an experimental point of view, Newburger[17] produced standardized celiotomy wounds in rats and at intervals of 3–5–10 days, the strength of the wounds were determined in the animals which were kept at rest and in others which were exercised. Exercise, rather than immobilization, was found to hasten the increase in tissue strength of the experimental abdominal incision. The Russian, Kimbarovskiy[18] studied wounds in dogs in the ambulant state, and dogs forced into the reclining position by means of plaster encasements. In the restricted animal, he concluded there was a decrease in fibroplasia.

The value of transverse or muscle-splitting incisions is clearly apparent. In a previous paper, Fisher and Burch[65] reported 1,500 appendicectomies through

a McBurney incision had no disruptions. Singleton and Blocker[1] report 470 transverse incisions in the upper abdomen, with no disruptions, and 292 verticals with nine disruptions. Rees and Coller[20] had 225 consecutive transverse incisions with no disruptions and only one hernia.

The technic of wound closure is of primary importance. The data clearly indicate that a continuous catgut closure of the peritoneum is followed by high rate of disruption. The importance of the peritoneum in maintaining the integrity of the abdominal wound is not sufficiently emphasized. The process of wound disruption does not proceed simultaneously throughout the wound.[21] On the contrary, it is a progressive phenomenon, starting with a giving-way of the peritoneum and the gradual protrusion of the viscera through the layers of the wound. Freeman[22] stresses the importance of the omentum acting as a wedge. When the skin stitches are removed, the slightest strain is enough to make the disruption complete. The fact that it was nearly complete at this time is shown by the appearance of the wound. Fresh bleeding is seen only in the skin. The deeper tissues do not bleed. They are edematous, matted together, and covered by glistening granulation tissue. It is usually obvious that the deeper separation is not recent.

The appearance of bloody drainage from an abdominal wound is suggestive of a dissolution of the peritoneal suture line.

To maintain the integrity of the peritoneum, Meleney and Howes[23] advocate a mattress type of suture in the posterior fascia and peritoneum over-sewn with a layer of fine catgut. The utilization of an interrupted suture in the peritoneum, combined with continuous catgut, has been effective in preventing peritoneal dissolution and subsequent disruption. The interrupted sutures must be placed fairly close together. We usually use three or four to the inch. If so placed, the continuous catgut may be safely eliminated. In a few cases, we have had an opportunity to open cases so closed, and the absence of adhesions along the peritoneal suture line was striking. While this valuable method is not in general use, its value has been recognized by Cave,[24] Hinton,[25] Meyer,[26] and others.

In conclusion, it may be said that early ambulation does not affect the abdominal wound adversely. The satisfactory wound healing, observed following early ambulation, may be attributable to a better nutritional state, as well as a lowered incidence of the many complications favoring disruption, such as vomiting, cough, distention, and urinary retention. It is a safe procedure of great benefit to the patient, and its possibilities in decreasing hospitalization are as yet unrealized.

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DISCUSSION.—DR. ALFRED P. JONES, Roanoke, Va.: I wish to record the use of what might be called a continuous interrupted suture for the closure of muscle and fascia in abdominal wounds. A large full-curved needle is tied to each end of a long strand of the desired suture material. The first stitch is taken transversely through fascia only at the

lower end of the incision and tied so as to leave the suture of equal length on each side of the knot. With one of the needles, a bite is then taken through fascia and muscle on the left and brought up to catch fascia only on the right. With the needle attached to the opposite end of the suture, a corresponding bite is taken through muscle and fascia on the right, coming through to catch fascia above on the left. A square knot is then tied. This brings muscle-to-muscle and accurately approximates fascial edges.

The procedure is repeated for the length of the incision. Each interrupted stitch is independent, with the added security of having no loose ends to become untied, except for the terminal knot at the upper end of the incision.

DR. R. ARNOLD GRISWOLD, Louisville, Ky.: Several years ago, I had the opportunity of having an herniorrhaphy on myself, which taught me something about the tension on abdominal wounds. Any of you who have had an abdominal operation realize the tension on the wound when coughing, sneezing, or on a bedpan. If you get up early, as I did, you will realize the tension is much less, sitting or standing, than trying to use a urinal or bedpan in bed. We have run a small series of cases, putting a balloon attached to a water manometer into the abdomen following clean abdominal operations. The intra-abdominal pressure with the patient lying still in bed is about 20 cm. of water. The movements incident to arising from bed, walking across the floor and sitting down in a chair, cause a change in pressure to no more than about 20 cm. of water. However, when the patient in bed strains on a bedpan, coughs, or sneezes, pressure rises to 80 cm. or above.

DR. ROY D. MCCLURE, Detroit, Mich.: I want to support Doctor Burch's paper, because for a number of years we have been using this method, early ambulation, with great satisfaction to us and to our patients. Having worked with Dr. Eugene Pool, in New York, from 1909 to 1912, opportunity was afforded to observe his patients who were given passive and active exercises in bed. There is no doubt that patients profited from this system, which was described in the J. A. M. A., **60**, 1202, 1913.

In 1938, I read a paper on femoral hernia before this association (ANNALS OF SURGERY, **109**, 987, 1939). I reported an operation on a very prominent man who had a strangulated femoral hernia; he refused to stay in bed, and had no complication. We have all had experience with babies and children who will not be quiet and who fight restraint. Their wounds heal solidly and hernia does not occur. We do not urge our patients to get out of bed; we give them the opportunity to do so and assume that they would rather go to the bathroom than use the bedpan. We prefer the transverse or oblique incisions, especially in gallbladder cases. We have a great many industrial hernia cases, and all are allowed bathroom privileges during the entire postoperative period.

DR. JOSEPH E. J. KING, New York, N. Y.: About 17 years ago, during a short visit to Nashville, I called on Dr. W. D. Haggard to pay my respects. He almost pulled me into his office and said he had something to tell me. He spoke of a celiotomy, which I believe was an hysterectomy, that he had performed several weeks earlier. He went in to see the patient on the second day postoperative and found her, in general, to be all right. He then looked at the dressing and noticed that there was a slightly yellow, wet spot about her buttocks about as big as "the bottom of a washtub." He stooped over and smelled it, thinking it might be urine, but there was no odor. He then took off the dressing and to his utter amazement found it to be "wringing wet." It was so wet he could squeeze fluid out of it. He inspected the line of incision and it appeared to be in perfect condition.

The next day the patient was not quite so well, but she was not sick. There was no more fluid on the sheet. The following day, *i.e.*, the 4th day postoperative, the patient was not doing well at all. Her temperature had risen to about 103° F. Doctor Haggard could not explain the wet spot on the sheet, nor the patient's condition. He took her to the operating room and removed the skin sutures. He found the wound beneath the skin completely separated with a knuckle of small intestine protruding through the musculature

and lying in a subcutaneous position. He freed the knuckle of intestine and resutured the incision. On the following day her temperature went to 105° F. and she died.

He went on to say that not more than three weeks later he had identically the same situation, but this time he knew what to do. He took the patient to the operating room immediately on the 2nd day, removed the skin sutures and found the same condition. He resutured the wound, and the patient made an uneventful recovery. He stated that he had never seen anything like these two cases before in his life, nor had he heard or read about such a condition.

It is well that he told me about these cases, for two or three months later I had a patient that presented the same picture. I informed the family physician about what should be done and told him what Doctor Haggard had told me. The family physician said: "The family would go crazy if you took that patient back to the operating room when he is no sicker than he is." I replied: "If we don't, the patient is going to die, because Doctor Haggard said so." He said he would assume the responsibility for the patient's condition. On the 4th day the patient was not doing well at all, his temperature had risen to about 103° F., and he did not look well. The family physician then said: "We must go ahead and see." I told him it was too late, but we took him to the operating room, opened the skin incision and found exactly what Doctor Haggard had described. The wound was resutured readily and the patient was returned to his room, but he died on the 5th day, with a temperature of 105° F.

About three months later the same family physician and I operated upon a patient whose story was identical with those described above. As soon as the doctor saw the wet spot on the bed he said: "Let's go!" We took the patient to the operating room, removed the skin sutures and found the same situation as described. The incision was resutured, and the patient made an uneventful recovery.

I have never seen another case like these two, and they were exactly as Doctor Haggard described his cases to me. I have related the story a number of times to colleagues from all over the country, and I have received 25 or 30 letters from some who have had the same experience. They told of meeting with the same resistance from the family physician but, instead of waiting, they resutured the wound immediately when the condition had been observed—always on the 2nd day—without loss of any of the patients.

In conclusion, should any of you ever see a large wet spot about the patient's buttocks on the 2nd postoperative day, and it does not smell like urine, I strongly advise that you immediately explore the incision.

Dr. Thomas O. Otto, Miami Beach, Fla.: Doctor Burch has presented an excellent paper. In wound closure the choice of suture material is of great importance, and early ambulation is of great benefit in the improvement of circulation and avoidance of postoperative complications. Since my return from the Service it has been my misfortune to encounter three cases of wound disruption.

One case, an infant seven days old with congenital hypertrophic stenosis, demanded prompt surgical intervention. Two cases in the seventh decades of life suffered gastric carcinoma, obstructing totally. All three cases were extremely malnourished and prompt surgery was indicated. The infant was closed with silk and the adults were closed with cotton. Immediate steps to correct avitaminosis and hypoproteinemia were instituted. All three cases showed serum protein levels of four, or less, at the time of surgery. Secondary closures with through-and-through silver wire sutures were carried out in all three cases. The infant and one adult survived and one adult succumbed. Wound healing was perfect in the two survivors after blood serum protein levels were built up to 6.5, or higher. Correction of the hypoproteinemia is of greater importance than the choice of suture material.

In cases of malnutrition and low serum protein levels the employment of through-and-through silver wire sutures as a prophylactic against disruption suggests itself, until avitaminosis and serum protein levels can be restored to normal.

DR. FRANK K. BOLAND, Atlanta, Ga.: This discussion reminds me of a case I had forgotten about. I am like the man who said there were three things he could not remember; one was people's names; one was people's faces; and the third—well, he had forgotten what the third thing was.

This is the case of a large lady upon whom I performed a cholecystectomy. I took the stitches out about the 8th day. I had to leave town that night and got back the next morning, and I generally look at the wound the day after the stitches are removed. Lo and behold! she was sewed up. I said: "I thought I took these stitches out yesterday; there must be some mistake about it." So I proceeded to remove them again. Then I found that she had disrupted during the night and Doctor Ferguson had gone in and sewed her up again, and the nurse had failed to notify me of the event. Doctor Ferguson's repair of the wound held good, although the sutures had been in place less than 18 hours.

DR. JOHN C. BURCH, Nashville, Tenn.: (closing): I want to thank you for the discussion. Early ambulation is but one phase of what may be called mobilization of the patient. In those who cannot immediately get out of bed, voluntary exercises are important. Early exercise will help in the prevention of thrombophlebitis and pulmonary embolus. These exercises must be started on the first postoperative day. In my opinion, retention sutures are of no value, and I have long since abandoned them. The through-and-through closure is a makeshift method and is followed by a high percentage of herniae and evisceration. Much progress can be made by greater utilization of the transverse incisions and the abandonment of continuous sutures of absorbable material.

WOUND CLOSURE WITHOUT THE USE OF GRAFTS*

THOMAS O. OTTO, M.D.

MIAMI, FLORIDA

SURGEONS have come to employ the word "closure" loosely and inaccurately. It is significant that the medical dictionaries do not include the word "closure." The term is clearly defined in standard dictionaries as "act of closing or shutting; that which closes or shuts."

The misuse of the word is particularly glaring in the numerous articles on wound closure written during the recent great war and following its happy conclusion. Some authors have gone so far that they describe closure of war wounds by the three methods of undermining, swinging flap grafts and split-thickness grafts. Other authors have described wound closure by the use of split-thickness grafts alone.

The purpose of this paper is to set forth the possibilities of wound closure anatomically and physiologically by two ancient surgical procedures, namely, the radical undermining of wound margins and interpolation. Interpolation is defined as the surgical transplantation of tissue.

Many thousands of war wounded returned to our hospitals were received with wounds quickly covered by split-thickness skin grafts. These cases have proven to be a great problem, and they are with us yet. In these cases definitive surgery was not permissible since the "successful takes" had broken down and such procedures as bone grafting, arthroplasty, neurolysis, and nerve repair could not be safely carried out. What appeared to be a quick "closure" has resulted in a great delay, inasmuch as Plastic Centers had to be established and the wounded transferred to these Centers for wound closure before wound repair could be accomplished. These delays in the restoration of function could have been avoided if the wounds had been closed early instead of merely covered.

In dealing with approximately 11,000 battle wounded, all wounds were closed by excision of the wounds, the radical undermining of the margins, and the employment of marginal flaps when necessary. Epithelial grafts were not employed except in the treatment of extensive burns which, fortunately, proved to be of small incidence.

Wound closure by the methods to be presented in this paper was carried out as early after injury as covering with grafts could be safely carried out. Less time was consumed in the closure than is normally required for the use of split-thickness skin grafts. By closure of wounds with adjacent full-thickness skin and superficial fascia a functional restoration was promptly obtained, and this permitted definitive surgery as soon as wound healing occurred.

* Read before the 58th Annual Session of the Southern Surgical Association, Hot Springs, Va., December 12, 1946.

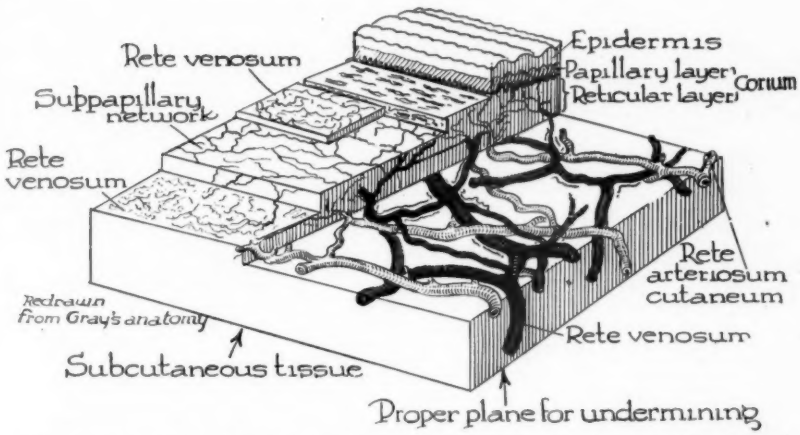


FIG. 1.—Anatomic diagram (redrawn from Gray's Anatomy, after Spalteholtz) showing origin and distribution of blood supply to the skin.

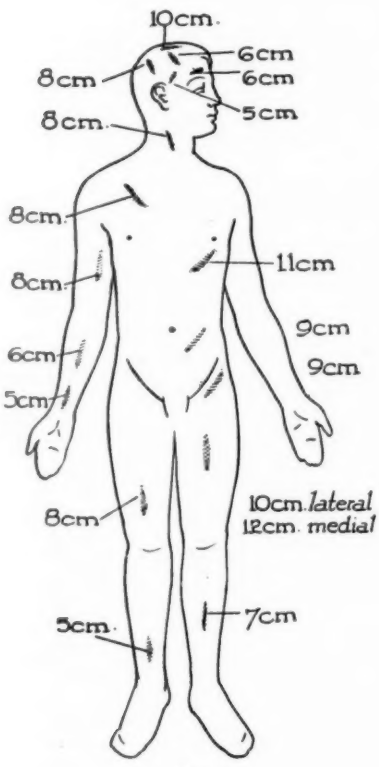


FIG. 2

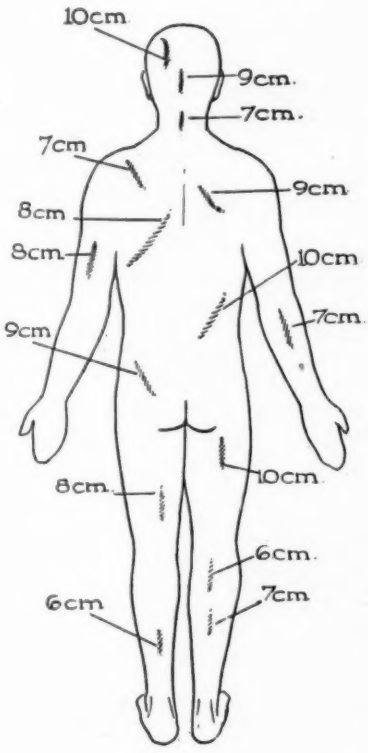


FIG. 3

FIG. 2.—Anatomic diagram (original) illustrating distances proven safe for radical undermining on anterior aspect of the body. (Not maximal)

FIG. 3.—Illustrating distances proven safe for radical undermining on posterior aspect of the body. (Not maximal)

These distances are not offered as the maximal and may well be exceeded in experienced hands.

Failure to appreciate the possibilities of wound closure by radical undermining and the use of marginal flaps has resulted in too timid employment of these methods. Fomon[1] in commenting on contiguous flaps states: "Although the principle governing this method originated in antiquity, its modern usage dates from 1830, when Larrey reintroduced it in Europe where it immediately gained popularity in the hands of such famous surgeons as Delpech, Dupuytren, Lisfranc, and Serre, and became known as the 'French flap.' While this

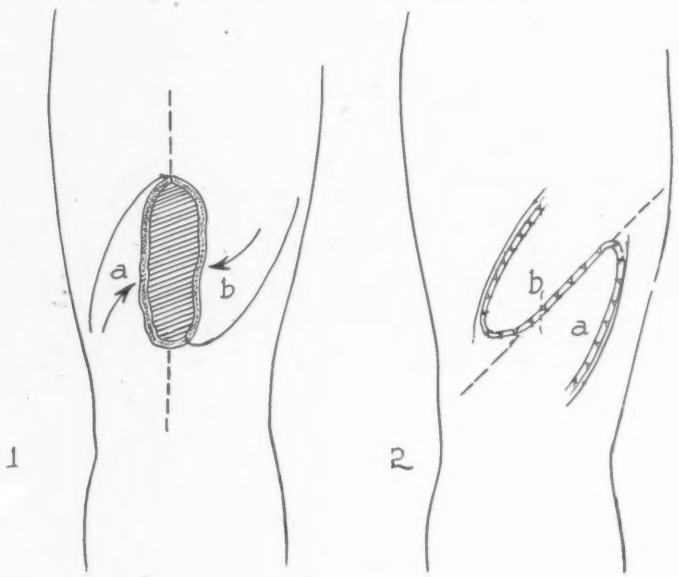


FIG. 4.—Diagrammatic illustration of interpolated marginal flaps with transposition. This affords closure by centripetal pull on margins, changing axis of the wound.

Note: The included angles of the cut marginal flaps must not be less than 20 degrees; nor greater than 45.

method has the advantage of simplicity, it is applicable only for minor defects and those in which the surrounding tissues are sound and sufficiently lax to permit of manipulation. In the case of large defects it would cause too great a distortion of the surrounding parts to warrant its use." This author, like most authors, has contributed to the failure to attempt wound closure by the employment of marginal flaps.

The skin is the largest organ of the body; it serves many important functions and comprises an area of 10 to 18,000 square centimeters; yet it does not possess an intrinsic blood supply. The skin derives its blood supply from the rete arteriosum and venosum which ramifies in the subcutaneous fascia and fat, and the subcutaneous fascia and fat, in turn, receives its blood supply

from the perforating vessels arising in the deep structures[2] (Fig. 1). The circulation of the skin consists of capillary branches of the rete arteriosum and venosum extending into its subpapillary layers. Undermining of the skin cannot be carried out to any extent without depriving the skin of its blood supply.

FIG. 5.—Case 1: Gunshot wound, right shoulder, 15 days duration. Single-stage closure by radical undermining with reconstruction of acromioclavicular joint. Healing 10 days.

Radical undermining of the wound margins can be safely carried out to a great extent if the undermining is conducted in the proper plane for mobilization. This plane is beneath the subcutaneous fascia and fat in every anatomic location. It is imperative not to injure the perforating vessels. This procedure is not difficult if the margins are elevated, and the mobilization is carried out by divulsion with scissors rather than by cutting; and if performed under direct vision. Hemostasis is not a problem; hematomata do not appreciably occur; and greater distensibility of the wound margins is obtained. This simple

procedure will, in itself, permit the closure of larger wounds than will slight undermining in an improper plane and pulling with sutures.

A search of the literature fails to give the distances to which undermining of the margins can be carried out safely. The anatomic diagrams (Figs. 2 and 3) illustrate the distances proven safe to undermine in the various anatomic

A

B

FIG. 6.—Case 2: Gunshot wound, severe, groin, scrotum, testicle and perineum, with transection of membranous urethra; 29 days duration. Single-stage closure by radical undermining, with repair of scrotum, testicle and urethra. Healing completed 14 days.

locations. These distances are not offered as the maximum which can be attained, and could well be exceeded in experienced hands.

In wounds that do not permit of closure after radical undermining, multiple-stage closure is practicable and repeated undermining and closure can be carried out at intervals as early as two weeks. Compensatory relaxation occurs

within that period and continues for months. Otto,[3] in dealing with subtotal avulsion of the scalp, has shown what can be accomplished by this method.

The second simple surgical procedure to be executed in wound closure without the use of grafts is the employment of marginal flaps. In wounds that cannot be closed after radical undermining because tension is too great across

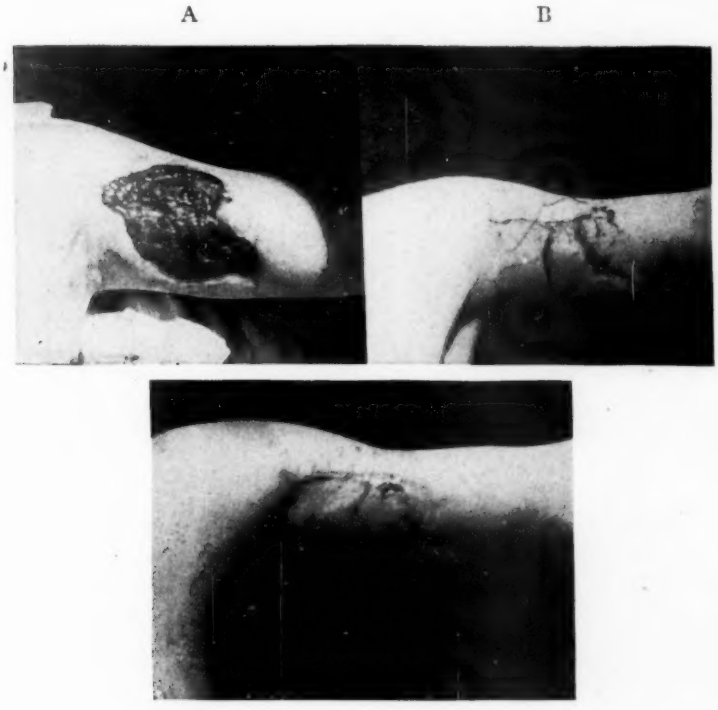


FIG. 7.—Case 3: Gunshot wound, arm, left, medial aspect; 17 days duration. Single-stage closure after radical undermining, with rotation of single marginal flap. Complete healing 7 days.

any given diameter, marginal flaps may be cut and rotated across the wound. This procedure affords closure by permitting of centripetal pull on the margins of the wound; it is illustrated in Figure 4. When cutting marginal flaps the included angle formed by the margin of the wound and the incision should not be less than 20 degrees. This insures circulation to the tip of the newly-formed flap. Nor should the angle be greater than 45 degrees to enable rotation across the denuded surface. The size and the number of marginal flaps to be employed is determined by the size of the wound to be closed.

The technical methods of closure discussed are to be carried out only after proper preparation of the patient. Shock must have been combatted, anemia

and hypoproteinemia corrected, blood serum level restored to normal, avitaminosis reduced and general and local sepsis controlled. The methods of accomplishing these results are too well-known to warrant repetition in this paper. The importance of carrying out this preparation of the patient cannot be overemphasized since normal wound healing does not occur if they are neglected.

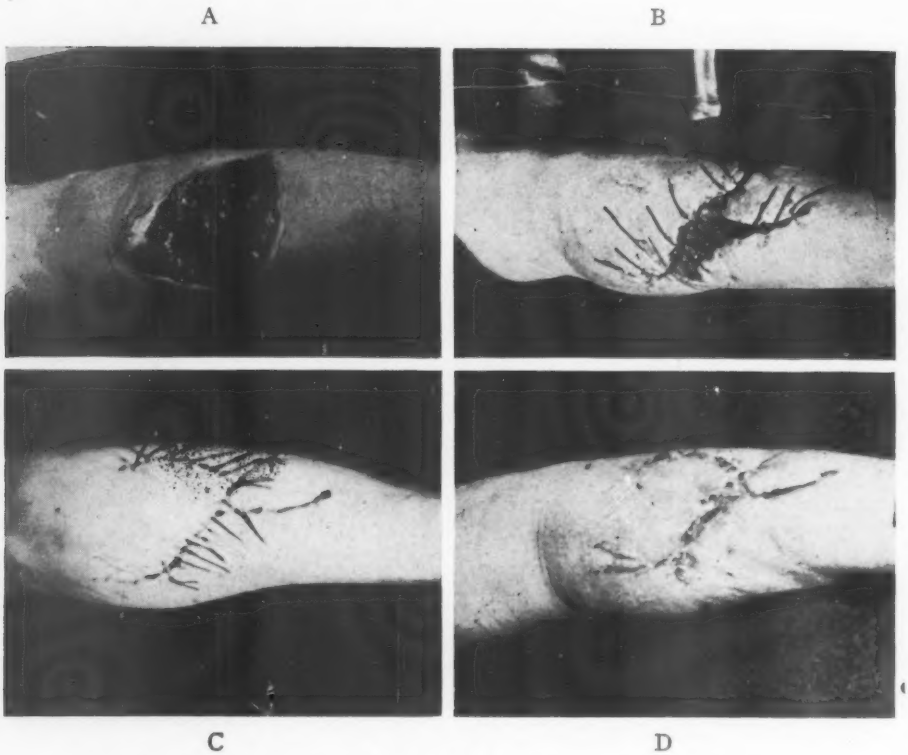
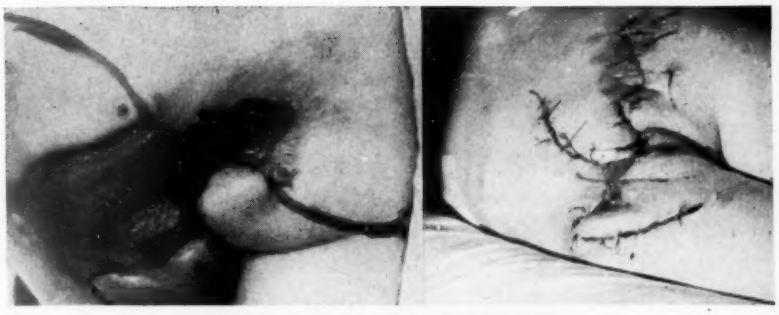


FIG. 8.—Case 4: Gunshot wound, leg, right, posterior aspect; subtotal loss of gastrocnemius and compound comminuted fracture fibula; duration 26 days. First stage: partial closure after radical undermining, with single marginal flap. Second stage: 14 days later, repeated radical undermining with complete closure. Complete healing 24 days.

Épluchage is the French term for complete excision of a wound. It demands a greater wound revision than simple débridement. In surgical preparation of wounds for closure by the described methods, épluchage is carried out. The skin margins are cut away vertically five to six millimeters proximal to the border of granulation. All granulation tissue is carefully removed by excision and curettage, since it is to be regarded as infected tissue and young scar tissue. Granulation tissue, the early tissue of wound repair, is young connective tissue. It consists primarily of capillary loops surrounded by fibroblasts which fuse with each other. The fibroblasts contract progressively to the

A B



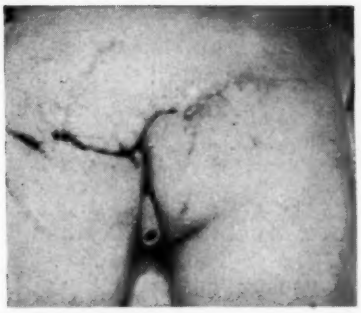


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FIG. 9.—Case 5: Shell fragment wound, severe, buttock, with loss of rectum, coccyx and lower sacrum; duration 63 days. Single-stage closure by radical undermining, with utilization of three marginal flaps. Devine colostomy previous to closure. Complete healing 14 days. Followed by reimplantation of rectum 17 days after first stage.

A B

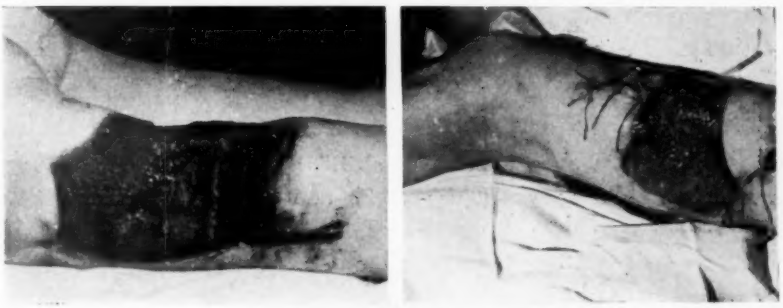

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FIG. 10.—Case 6: Shell fragment wound thigh, left, posterolateral aspect, with extensive loss of vastus lateralis and hamstring muscles; duration 39 days. First stage: partial closure by radical undermining and two marginal flaps. Second stage: 15 days later, radical undermining and employment of marginal flap from posteromedial aspect of thigh. Third stage: 17 days later, radical undermining and employment of marginal flap from gluteal region. Fourth stage: 30 days later, radical undermining of margins and closure completed. Total elapsed time for closure and healing, 73 days.

formation of scar tissue which becomes increasingly avascular if left in the wound.

In the approximation of the freshly cut margins after mobilization and interpolation, sutures are to be used judiciously. Tension sutures are spaced three to four centimeters and include two to four centimeters of the flap. Skin approximation sutures are spaced one and one-half centimeters, and are alternately of the end-on mattress type to prevent inversion and eversion. They should be placed 15 to 20 millimeters from the wound margins. In large wound closures small Penrose drains have been employed. Compression bandages with elastic wrapping are applied to control oozing and to splint the tissues. When indicated, plaster splints are used for immobilization.

Closures accomplished by these methods are shown photographically in Cases 1, 2, 3, 4, 5 and 6.

SUMMARY AND CONCLUSIONS

1. Secondary closure of wounds is possible in the vast majority of cases if the principles discussed are thoroughly understood and carried out.

2. Simple surgical procedures applicable for secondary wound closure without grafts are reviewed.

3. Multiple-stage closures can be safely employed.

4. Results of secondary wound closure by these methods restores normal functions, and permits of definitive surgery in a shorter elapsed time.

5. The diagrams (Figs. 2 and 3) show the distances proven safe for mobilization in different anatomic locations.

6. The advantages of wound closure without the use of grafts has been rationalized.

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DISCUSSION.—DR. JOHN STAIGE DAVIS, Baltimore, Md.: Doctor Otto's paper has brought to our attention, again, the very important fact that many extensive wounds can be closed without the use of skin grafts. Since the development of the dermatome, skin grafting has been done by many men who could not previously cut a graft, and it has been thoroughly overworked. Skin grafting has been done in many cases where it should not be done. I should say that, roughly speaking, 50 per cent of the wounds that are skin grafted could be closed by some such method as has been demonstrated by Doctor Otto. It is well to realize that skin-closing and wound-covering with grafts are different things, and the latter frequently leaves an area very difficult to deal with and one which it not functionally satisfactory. A wound closed by suture of the subcutaneous tissue and the skin always gives a very much better functional result.

DR. ROBERT IVY, Philadelphia, Pa.: I wish to thank the Association for inviting me to the meeting and allowing me the privilege of discussing Doctor Otto's excellent paper.

I am in entire agreement with him and with Dr. Staige Davis about closure of these wounds by undermining the local skin and subcutaneous tissue whenever possible, without the use of skin grafts. In some extensive wounds, too large to be closed by this method, a marginal flap can be used, and the raw area that is left by sliding over the flap can then be covered by a skin graft, so that the graft will not be on the site of the original wound. Doctor Otto spoke of the frequency with which grafts used on these wounds break down, but even though they heal well they do not provide a satisfactory soft tissue bed for later orthopedic or neurosurgical procedures.

In the correction of scars and lesions about the face where the cosmetic result is important, the use of local tissues by undermining and formation of sliding flaps, after multiple excision of the scar or growth, has been emphasized by Ferris Smith in preference to covering the raw areas with grafts, which may be unsightly and many times do not provide the proper contour.

DR. J. ALBERT KEY, St. Louis, Mo.: I am very happy to hear this paper, because many young surgeons in the Army who had dermatomes had to use them, and they did use them. Everything that could be grafted was grafted. They are getting to be the same in civil life.

There is another factor besides the dermatome which has led to an epidemic of skin grafting; that is, the undue emphasis put on never closing a wound with tension. The reason we have strong suture material is to pull them tight when necessary. It is amazing, if you strip a flap from the deep fascia by blunt dissection, how much stretch can be obtained. That is not good surgery to some of you people, but it works. We should get away from this idea of not suturing wounds with tension.

DR. THOMAS O. OTTO, Miami Beach, Florida (closing): I want to thank Doctor Davis, Doctor Ivy and Doctor Key for discussing my paper. Doctor Key's use of blunt dissection for undermining, rather than undercutting, conserves the peripheral blood supply. One must undermine beneath the subcutaneous fascia and fat if the blood supply to the skin is to be conserved.

BILATERAL CUTANEOUS URETEROSTOMY EIGHTEEN YEARS AFTER URETEROSIGMOIDOSTOMY FOR EXSTROPHY OF THE BLADDER*

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URETERO-INTESTINAL ANASTOMOSIS has been utilized as a means of diverting the urinary stream in exstrophy of the bladder and a variety of other incapacitating vesical lesions. Since Simon[1] first suggested and carried out uretero-intestinal anastomosis for exstrophy of the bladder in 1815, numerous methods for performing the operation have been devised. Original technics have been modified many times in an effort to obtain more satisfactory results. The age at which operation is performed is thought to bear some relationship to the complications which arise from ascending infection of the kidneys. The present tendency is to operate early, preferably within the first six months of life, before the bacterial flora of the bowel become too varied and pathologic. Higgins[2] reported 17 cases of infants operated upon when less than one year of age. He felt that the incidence of pyelonephritis in this group was less than if the operation had been deferred until an older age. Two of the 17 died during the postoperative period. The age at which the operation is performed does not, of course, eliminate such mechanical factors as angulation and stricture formation at the site of anastomosis, factors which most likely account for the majority of complications encountered in these cases.

From a review of the literature it is difficult to determine the percentage of patients who remained well for a period of years after ureterosigmoid anastomosis. In the majority of reports, statements as to the general health of the patient are vague and data concerning renal function tests are not sufficient to be helpful. By combining the reports of 13 authors[3-15] we were able to collect 41 cases of uretero-intestinal anastomosis in which the status of the patient could be evaluated (Table I). An analysis of the 41 collected cases, and our own case, revealed that these patients were alive from six to 44 years after operation. Sixteen patients, or 38 per cent, were reported as "well" and by "well" we assume that there was no clinical evidence of renal infection or insufficiency. In the remaining 26 cases, or 62 per cent, the following conditions were encountered: hydronephrosis, 21 times; loss of function of one kidney, eight times; renal calculi, seven times; calculous pyonephrosis necessitating nephrectomy, two times; and infected hydronephrosis requiring

* Read before the 58th Annual Session of the Southern Surgical Association, Hot Springs, Va., December 11, 1946.

TABLE I

ANALYSIS OF 41 CASES OF URETERO-INTESTINAL ANASTOMOSIS

Collected from the Literature

Author	Age at Op. Years	Years P. O.	Status of Urinary Tract
Estor[3] (1926)	1 5/12	24	Well
Middleton[4] (1931)	17	20	Blood urea nitrogen 32 mg. %. Urograms mild hydronephrosis.
Walters[5] (1932)	25	15	I. V. urograms normal. Blood urea nitrogen normal.
Foulds[6] (1933)	4	26	19 yrs. postop. Right calculus pyonephrosis and perinephric abscess. Left renal calculus passed spontaneously, with rupture of lower ureter and death. Blood urea nitrogen 83.7 mg. %.
	11	25	Well
Allison[7] (1933)	7	20	Blood urea nitrogen 26 mg. %. Left calculus. Pyonephrosis and perinephric abscess. Dead left kidney.
Estes[8] (1934)	5	22	Died in uremia—Autopsy: Contracted kidney; Thickened ureters.
Falk[9] (1938)	7	25	Right nephrectomy for pyonephrosis—Left kidney normal.
Fisher[10] (1938)	16	22	Blood urea nitrogen 91 mg. %—Died—Autopsy: Bilateral pyonephrosis and pyoureter.
Wade[11] (1939)	3	35	Renal function tests and I. V. urograms normal.
	10	28	Left renal calculus passed spontaneously. Blood urea 48 mg. %.
	27	12	Hydronephrosis and hydroureter
	17	13	I. V. urograms showed normal function.
Hepler[12] (1940)	8	15	All living and well—by well, author states patient is healthy, has no clinical evidences of persistent renal infection or insufficiency and no marked changes in the ureters or kidney pelves.
	7	15	
	5	14	
	6	13	
	38	14	
	36	11	
Stevens[13] (1941)	16	26	NPN 38, PSP 1 hr. 25%. Marked left hydronephrosis. 2 episodes of infection requiring bed care.
	22	7	Recurrent urinary infection. Died.
	49	11	NPN 53. PSP 10% 1 hr. Right hydronephrosis.
	28	6.5	NPN 35. PSP 20% 1 hr. Urograms dilatation rt. ureter pelves. Left incompletely outlined.
	15	11	NPN 34. PSP 45% 1 hr.
	36	6	Dendritic calculus. NPN 128. Died.
	6	44	Renal calculus. Died.
Turner[14] (1943)	8	30	Apparently well.
	22	29	Calculi requiring removal 24 yrs. after.
	19	25	Apparently well.
	6	25	Right renal calculus removed 14 years after.
	5	23	Renal pain 22 years after.
	10	19	Apparently well.

TABLE I—*Continued*

Author	Age at Op. Years	Years P. O.	Status of Urinary Tract
	8.5	17	Nephrectomy for pyonephrosis.
	3	16	Apparently well.
	3.5	16	Apparently well.
Lower[13](1943)	10	22	Recurrent renal infection. Blood urea 48 mg. %. Negative urograms.
	3.5	18	Blood urea 51 mg. %. Left hydronephrosis. Dilatation of right ureter.
	23	21	45-minute urograms. Right hydronephrosis. Left excreted very little dye. Blood urea 51 mg. %.
	22	21	Blood urea 42 mg. %. Urograms showed normal renal pelves.
	30	18	Nonfunctioning right kidney. Blood urea 54 mg. %.
	18	27	Normal right kidney with right hydroureter. Left kidney fails to visualize. Blood urea 54 mg. %.

nephrostomy, two times. These conditions obviously assume the same importance as they do when encountered in individuals who have an otherwise normal urinary tract. Defective drainage from cicatricial stenosis of the intestinal anastomosis is largely responsible for the late appearance of dilated ureters, hydronephrosis, recurrent infections, stone formation and impaired renal function encountered in these cases. The pronounced dilatation of the ureters precludes reimplantation to the sigmoid, so that cutaneous anastomosis appears to us the most desirable alternate.

If the small series of cases evaluated above constitutes an index to the whole picture, it is apparent that the late results in more than half of these cases are unsatisfactory. In this report we are chiefly concerned with this group. It is our purpose to show that the life expectancy of certain patients selected from this group may be improved by uretero-cutaneous anastomosis and to report such a case.

Case Report.—C. D. M., a 30-year-old white man, was first seen in the Ochsner Clinic, August 20, 1945, with the chief complaints of renal discomfort and recurrent chills and fever.

At the age of 12 years bilateral uretero-intestinal anastomosis (Coffey-Mayo operation) was performed by Dr. C. H. Mayo for exstrophy of the bladder. One year following the operation the patient began to have pains in the left flank associated with nausea, chills and fever. These symptoms subsided when the patient was given a purgative. They recurred, however, at intervals of about six months. These episodes continued until the early part of 1940, when the left-sided renal pain subsided and has not recurred. At about this time, however, the patient began to have pain in the right side associated also with chills and fever. His capacity for work during the past five years has become increasingly limited.

A year before the patient consulted us his local physician made an excretory urogram which was said to show the right kidney and ureter to be in good condition but the left kidney and ureter were not visualized. At that time, specimens of urine obtained from the rectum revealed pus but no blood. The patient was given sulfonamides and mandelic acid, which had no tendency to control the acute episodes of urinary infection. Instead,

FIG. 2.—Forty-minute excretory urogram on admission revealing right hydronephrosis with hydro-ureter and only faint trace of dye on the left.

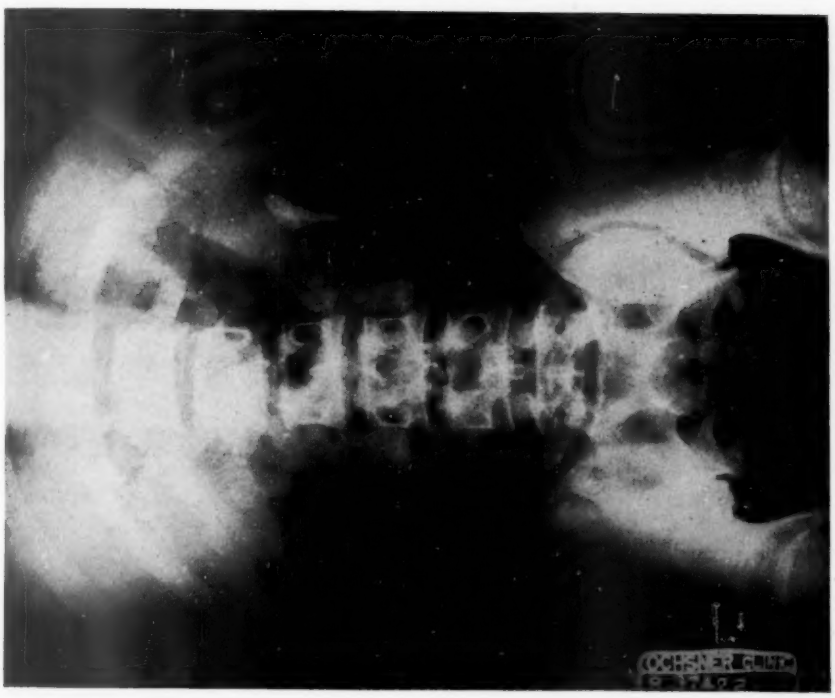

FIG. 1.—Plain roentgenogram on admission revealing calculus in left kidney.

they recurred with increasing frequency. The most recent attack occurred two weeks before we saw him and was characterized by pain in the right flank, chills and fever.

The patient was able to have intercourse with difficulty but has ejaculations. His appetite was fair and bowel movements were regular.

The patient was a well-developed, fairly well-nourished, intelligent white male, somewhat pale but not acutely ill. He weighed 135 pounds. At examination, both kidneys were palpable, and the right was moderately tender. Three scars from previous operations marked the lower part of the abdomen. There was complete epispadias. Rectal examination disclosed no mass which could be identified as prostatic tissue.

Examination of the blood revealed 5,300,000 red blood cells, 15.5 Gm. hemoglobin, 8,400 white blood cells, 75 per cent segmented cells and 25 per cent leukocytes. Blood urea nitrogen was 20 mg. per cent.

FIG. 3A.—Mathé collecting apparatus in position on the patient.

Plain roentgenograms of the urinary tract showed a calculus, measuring 4 cm. in length by 0.5 cm. in width, in the left renal pelvis (Fig. 1). The excretory urograms revealed slow concentration of the diodrast on the right side and showed a fair outline of the pelvis and calices in 40 minutes disclosing blunting of the calices and marked dilatation of the pelvis and ureters (Fig. 2). The left kidney showed only a faint trace of the dye in the forty-minute film.

The patient was put on a maintenance dose of mandelic acid in an attempt to control the urinary infection. He returned in two months for reëxamination and reported that he had not had fever in the interval. Excretory urograms showed no change from the previous films. The blood urea nitrogen had risen to 25 mg. per cent, and the patient had lost five pounds in weight.

It was felt that surgical intervention was indicated in order to remove the obstruction to drainage at the site of anastomosis. Accordingly, November 26, 1945, bilateral cutaneous ureterostomy was done. Under spinal anesthesia a right lateral abdominal incision was made, the old scar being excised. The muscle and fascia were divided and the peritoneum with its contents was retracted medially. The right ureter was found to be about 2.5 cm. in diameter, with a very thin, almost transparent wall. There was

little evidence of periureteritis. As the ureter approached the peritoneum, it narrowed down considerably, and there were dense adhesions around this junction. These were not disturbed. The ureter was divided just outside the peritoneum. The distal stump was ligated with a transfixed No. 2 chromic catgut suture and the proximal stump was freed

FIG. 3B.—Mathé collecting apparatus in position on the patient.

FIG. 3C.—Ureterostomy stumps demonstrating adequate rosette of ureter beyond the skin margin.

from its bed and brought up into the wound. A No. 16 Robinson catheter passed easily up the ureter to the renal pelvis. This catheter was left in place. One Penrose drain was inserted into the lower angle of the wound, and the wound was closed in layers, with catgut for muscle and fascia and silkworm and dermal for the skin, care being exercised

not to constrict the ureter. No difficulty was encountered in obtaining a good length of ureter beyond the skin margin.

A similar procedure was carried out on the left side. The ureter was about 2 cm. in diameter and not particularly distended. Only a little urine escaped when it was opened. There was also very little periureteritis on this side. The ureter was severed close to its peritoneal entrance, the distal stump was transfixed as on the right, and the proximal stump was freed from its bed and brought up into the wound. A long stone forceps was easily introduced up the ureter to the renal pelvis in an attempt to remove

FIG. 4.—Excretory urogram five months after operation revealing considerable improvement in hydronephrosis and concentration of dye.

the stone noted in the plain roentgenogram. This could not be accomplished, however, as the stone had slipped down into the lower calix. A No. 16 Robinson catheter was passed up to the kidney with ease, and left in place. The wound was closed, the ureteral stump being brought well beyond the skin surface as on the right. The patient's postoperative course was uneventful. It was noteworthy that at first only about one-sixth as much urine was excreted from the left kidney as from the right. The ureteral stumps healed excellently.

Approximately two weeks after the operation an indigo carmine test was done; the dye, injected intravenously, appeared from the right ureter in excellent concentration in three minutes, and from the left ureter in ten minutes in about 50 per cent of the normal

concentration. The patient was fitted with a Mathé-type of collecting apparatus and discharged from the hospital (Fig. 3a, 3b, 3c). His ureters were functioning well and retention ureteral catheters were not required.

The patient reported for a check-up five months after the operation. During this interval, he had gained 15 pounds in weight. His general health had improved, and he was entirely free of urinary symptoms. Excretory urograms at this time revealed a great reduction in the size of the hydronephrosis on the right side, with some improvement of function (Fig. 4). There had been considerable increase in excretion of the dye on the left, which indicated improvement of function of the left kidney. There had, likewise, been an increase in the size of the calculus in the left kidney which, in itself, is

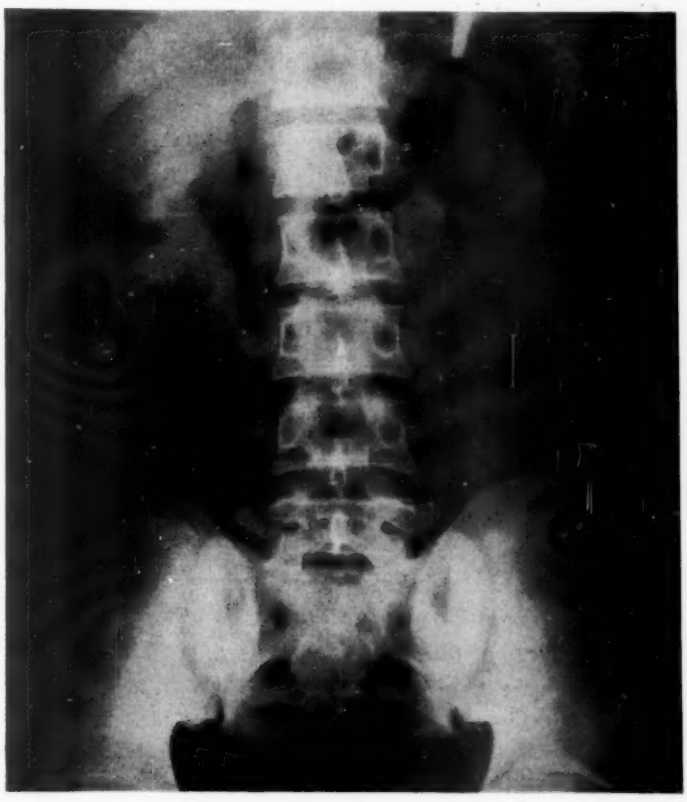

FIG. 5.—Excretory urogram 11 months after operation revealing further improvement in hydronephrosis and in concentration of dye by both kidneys.

indicative of improved renal function. On July 5, 1946, the stone was removed from the left kidney, and recovery was uneventful.

The patient reported for reëxamination October 15, 1946. His general health was excellent. His weight was 160 pounds, a gain of 25 pounds over his weight on admission. He was doing full-time work as a bank clerk, and during the summer season was the pitcher for his local softball team. Excretory urograms showed further improvement in the function of the kidneys (Fig. 5).

DISCUSSION.—The advantages expected to be derived from transferring the ureters to the skin in this case were (1) relief of back pressure on the kidneys; (2) control of urinary infection; (3) improvement of renal function; and (4) restoration of the patient to economic usefulness. All of these were accomplished and, in addition, we were able to prevent some of the disagreeable features often associated with cutaneous ureterostomy. The patient's ureters function well without catheters. He wears his apparatus with comfort, and is able to keep dry during both day and night.

One of the most unfortunate complications of cutaneous ureterostomy is to have the end of the ureters slough down to, or below, the skin margin. In such cases disagreeable strictures form. These are painful and hard to keep open. On one or two occasions we have immediately dissected down to viable ureter and brought it out to a higher level in order to get a good length beyond the skin surface. This may not be possible in all cases and nephrostomy may occasionally be required. Attempts are always made to prevent this complication by the observation of several well-recognized rules. The ureter should be freed from its bed without stripping in order to avoid injury to its blood supply. It is brought out without tension or angulation and allowed to project 4 to 5 cm. beyond the skin margin. The wound is closed lightly around the ureter and no stitches are placed in the ureteral wall. A suture in the ureteral wall will damage the blood supply and is not necessary if the length of ureter is adequate. The catheter used during the immediate postoperative period should be small enough to fit loosely in the ureteral lumen.

With respect to prognosis following ureterocutaneous anastomosis there is a scarcity of such reports in the literature. However, Keyes[16, 17] reported cases of patients living from 13 to 22 years after cutaneous ureterostomy for intractable tuberculosis of the bladder. Other similar reports may be found. It is reasonable to assume that the prognosis of more benign lesions would be equally as good. We are not suggesting that cutaneous ureterostomy will be indicated in a large number of cases following uretero-intestinal anastomosis. However, a review of the literature reveals that in many patients severe urologic lesions develop in the years subsequent to uretero-intestinal implantation. We believe that relief of the mechanical obstruction at the terminal end of the ureters by transferring the ureters to the skin will undoubtedly prolong the life of many of these patients.

SUMMARY

The literature on the late results of uretero-intestinal anastomosis has been reviewed in an attempt to evaluate the renal status in patients many years after operation. It is suggested that detachment of the ureter from the sigmoid and reimplantation into the skin as a means of relieving mechanical obstruction to the urinary flow will prolong life in the late stages of uretero-intestinal anastomosis. Such a case is reported.

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DISCUSSION.—DR. LEO BRADY, Baltimore, Md.: I think this is a very important and interesting contribution. Unfortunately, we do at times get in trouble after implanting the ureters into the large intestine, but as our technic has improved these complications have become less frequent. The new drugs, such as sulfathaladine, and the improvement in the operative technic have been helpful.

I should like to mention one patient whose convalescence has been very satisfactory. She had a papillary carcinoma of the bladder which did not respond to fulguration, radium or roentgen ray. I removed the entire bladder and implanted the ureters into the rectum, using the Coffee No. 2 operation. It has been four years since the operation was performed and her general condition has been excellent. There are no complications, and she voids only twice a night. The intravenous pyelogram is absolutely normal and there is no dilatation of the kidney pelves or the ureters.

Doctor Burns' paper is very instructive and helpful. In the future when I have a patient whose ureters I have implanted into the rectum and whose ureters and kidney pelves show progressive dilatation, I shall remember Doctor Burns' case.

OBITUARIES

GEORGE P. MULLER

1877 - 1947

For twelve years a member of the Editorial Board of the ANNALS OF SURGERY, Dr. George P. Muller died at his home in Margate, N. J. on February 18, 1947, following a short illness.

Doctor Muller was born in Philadelphia in 1877, and in 1899 received his medical degree from the University of Pennsylvania Medical School and

Dr. George P. Muller

continued with the University through successive positions as assistant instructor, instructor associate and professor of clinical surgery until July, 1933. For 13 years during this period he was also Professor of Surgery in its Graduate School of Medicine. In 1937 he became Osler Professor of Surgery at Jefferson Medical College, which position he held until 1946. Doctor Muller served as consulting surgeon to Rush Hospital and White Haven Sanatorium, and at Lankenau and Misericordia Hospitals, and was a past president of the Philadelphia County Medical Society, the Philadelphia Academy of Surgery, the College of Physicians of Philadelphia and the American College of Surgeons.

In 1935 when the Editorial Board of the ANNALS OF SURGERY was formed, Doctor Muller joined with a group of other outstanding surgeons from all parts of the country to help maintain the publication in the honorable position established for it by its founder, Dr. Lewis S. Pilcher, whose son, James, was Managing Editor until his recent death.

As a frequent contributor to the surgical literature, Doctor Muller brought to the ANNALS OF SURGERY the sound surgical and literary ability which had long been manifest during his distinguished career. The Board and the publishers will miss his wise counsel in the selection and appraisal of articles for this publication, and acknowledge great credit to him in helping to make the ANNALS of increasing value to the student and to the growing number of young men rising into the specialty of surgery.

JAMES TAFT PILCHER
1880 - 1947

Another great loss to the Editorial Board of the ANNALS OF SURGERY was suffered with the passing of Dr. James T. Pilcher, who died at his home in Brooklyn, N. Y. of a heart attack on April 6, 1947, a day following his 67th birthday.

Dr. James Taft Pilcher

Son of Dr. Lewis S. Pilcher, founder of the ANNALS OF SURGERY, James Pilcher was Managing Editor of the publication from 1935 until his death. His devotion to the standards set up by his father and carried on by the initial

board appointed in 1935 was manifest in the keen, critical interest he brought to this work. As a surgeon with a career covering two years on the staff of the Mayo Clinic, commanding officer of the 108th Field Hospital in France during the first World War, and a practice in surgery for over 40 years in Brooklyn, Doctor Pilcher's diligence and industry in preparing papers for publication did much to make the ANNALS OF SURGERY of such increasing value to the surgical specialty. His editorial conscience was ever on the alert for uniformity and accuracy in styling, he was always eager to track down new spellings, to confirm changes in nomenclature, and to put his best surgical judgment to the task of making the pages of the ANNALS of even excellence. The contributors who depended upon him and the other editors on the Board, with whom he was so closely associated, will miss him greatly.

Doctor Pilcher received his medical education at Columbia University and was a visiting surgeon to the Wycoff Heights Hospital and Evangelical Deaconess Hospital and had been Director of Urology at Downtown Hospital, New York, and attending surgeon at the Brooklyn State Hospital and Unity Hospital. In the first World War, he held the rank of major in the Medical Corps and received the Distinguished Service Medal.

NEW EDITORIAL ADDRESS

Original typed manuscripts and illustrations submitted to this Journal should be forwarded prepaid, at the author's risk, to the Chairman of the Editorial Board of the ANNALS OF SURGERY.

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Contributions in a foreign language when accepted will be translated and published in English.

Exchanges and Books for Review should be sent to Dr. Gibbon at the above address.

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